DISEASES OF THE BASAL GANGLIA
THEIR RELATION TO DISORDERS OF MOVEMENT*

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I

THE term basal ganglia has no precise limitation, having been used by the older anatomists for the large grey masses at the base of the brain, including the optic thalamus. In the present century the thalamus has been excluded, and the use of term limited to the caudate nucleus, the putamen, and the globus pallidus. For neuropathological reasons certain closely related subthalamic nuclei are often included. I shall not here discuss the intricate, and in part disputed, interconnection between these structures. The most important of these are shown diagrammatically in fig. 1, which is designed to emphasise the reflex pathway from the intralaminar (I.L.) and centrum medianum (C.M.) nuclei of the thalamus to the globus pallidus, putamen, and caudate nucleus, and the efferent connections of these nuclei with the subthalamic nucleus (S.), the reticular formation of the midbrain (M.B.R.), and the substantia nigra (S.N.). Short pathways connect these scattered subthalamic structures with the important motor reticular formation of the brainstem. The caudate nucleus, putamen, and globus pallidus also receive pathways from various areas of cerebral cortex. The caudate nucleus contributes an important pathway to the lateral thalamus. Though the basal ganglia are closely interrelated with the cerebral cortex in this way, they preserve both structure and function in its absence. This independent reflex activity is responsible for much of the behaviour that distinguishes the decorticate from the decerebrate animal.

My first objective is to define the degree to which diseases affecting the different ganglia produce consistent physical signs. Before 1895 there was no hint that damage to this region of the brain had any specific effect, though in the time of Hughlings Jackson it was customary to regard the basal ganglia as the seat of regulation of those simple spasms that remain when the cerebral cortex is destroyed. The first hint that specific disorders of movement are related to limited disease of these ganglia appears to have been the excellent description of congenital double athetosis by Anton in 1896, with the related scarring of the outer putamen on both sides. The most convincing demonstration, however, was the description of progressive lenticular degeneration by Kinnier Wilson (1912), providing a dramatic demonstration of the relation of limited lesions of these ganglia to rigidity, distorted posture, and tremor. Only then did the earlier descriptions of outfall of nerve-cells in the globus pallidus in paralysis agitans by Jelgersma (1908), and the comparable atrophy of the caudate nucleus in Huntington's chorea described by Alzheimer (1911), assume real significance.

As had so often happened in relation to clinicophysiological correlation in cerebral disorders, the rush to stake out claims on the anatomical terra nova outran both the available physiological philosophy and the necessary neuropathological experience. Indeed the Croonian lectures of Kinnier Wilson (1925) are wholly devoted to a sobering criticism of the massive superstructure that had already burdened the topic. The difficulties that pervade the subject are derived from the very general nature of the pathological processes that affect these structures, the kaleidoscopic variations in resulting symptomatology, and the poorly understood part that the ganglia play in normal cerebral function.

Hepatolenticular Degeneration

The striking demonstration of lenticular cavitation in hepatolenticular degeneration (Wilson's disease), though important in other respects, was most misleading in its implication that the disease process was itself localised. The widespread nature of the gliosis that accompanies all forms of the disease (Hall 1921) is now generally recognised. That the disease is an inborn error of metabolism resulting in accumulations of protein-bound copper in many organs, particularly the liver and nervous system, is also well understood. Within the nervous system greatly increased concentrations of copper are present in the putamen and thalamus, and to a less extent in the cerebellum and cerebral cortex (Cumings 1948, Spillane et al. 1952, Cartwright et al. 1954). The striking improvement that can follow removal of small amounts of copper from the body by chelation indicates that, in some cases, a

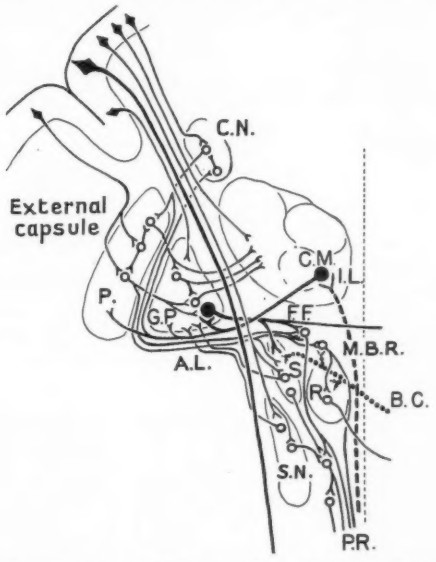


Fig. 1—Diagram of the chief connections of the basal ganglia.
The efferent systems of the globus pallidus (G.P.), putamen (P.), and caudate nucleus (C.N.) pass through the ansa lenticularis (A.L.) to the fields of Forel (F.F.). There they reach the subthalamic nucleus (S.), the scattered nuclei of the midbrain reticulum (M.B.R.), substantia nigra (S.N.), and red nucleus (R.), with connections to the reticular nuclei of the pons (P.R.). The reflex circuit has an afferent limb in the lemniscus and ascending tegmental tracts (represented as a broken line) through the intralaminar (I.L.) and central (C.M.) nuclei of the thalamus. The midbrain and subthalamic reticular nuclei receive terminations of the brachium conjunctivum (dotted line B.C.).

* From the Croonian lectures for 1960, delivered before the Royal College of Physicians of London on Feb. 23 and 25.

relatively small fraction may in time interfere with vital enzyme function. In the juvenile type such improvement is unfortunately offset by other unknown factors.

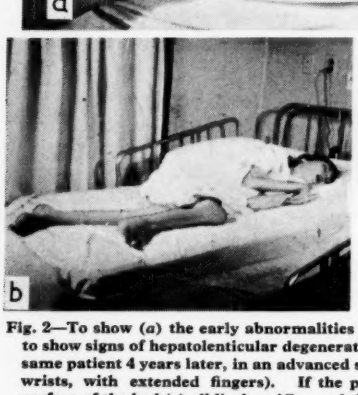
When the symptoms start after the age of 20 the disorder appears as flapping tremors at the wrist and shoulders, which are absent at rest and provoked by movement. The very diffuse gliosis of the nervous system that is then present makes it impossible to relate such incoordination to damage to any particular structure. The tremor has some features in common with that caused by other types of damage to the midbrain reticulum. The fate of such cases is usually determined by the severity of the associated hepatic cirrhosis. If they survive for long a generalised mild muscular rigidity ultimately appears in all limbs, predominantly in flexion, in association with severe dysarthria and dementia. There is then widespread fibrosis of the cortex, thalamus, and basal ganglia.

In the juvenile types of Wilson's disease involuntary movements of a different kind occur. These are at first small involuntary lapses in posture. At or about the same time the natural facial expression changes, the mouth is held more constantly open, and the eyelids blink seldom. The changes in expression, associated with slight postural changes in the hands in the nature of overextension of the fingers (fig. 2*a*), long precede the dysarthria and facile smile that were noted by Wilson. Gradually the postures of the limbs become more stiff—at first in walking, when they tend to overextension first on one side and then on the other—leading to an awkward clumsy gait. A plastic rigidity is then apparent in the affected limbs. It is at this time that a slurred dysarthria is usually first noticed. As the disorder progresses first one then the other arm becomes flexed in a hemiplegic posture, and the lower limbs become more constantly extended. As these postures develop, tremor usually appears. In some patients the tremor is that of the adult type of the disease, a rapid alternating flapping at the wrist and fingers. In others it begins as athetosis, with slow swings from overextension of the hand to overflexion. In this type the swing of movement may in time accelerate and make gradual transition into a parkinsonian type of tremor. In most patients the swings of athetoid movement become slowed by increasing rigidity; the hand becomes more continually flexed and the ankles overextended as part of the terminal hemiplegic dystonia that was illustrated so well in Wilson's original description.

I should like to draw particular attention to the evolution of the terminal dystonic state in hemiplegic attitude, for this has, in my experience, been invariably present when bilateral rarefaction or frank cavitation of the putamen has occurred. In time there is yet a further change in the symptomatology, in the nature of lessening of the hemiplegic rigidity, and its conversion into a state of mild general flexion (fig. 2*b*), with flexed wrists and extended fingers and ankles. If the patient is lifted from the bed, the limbs still stiffen, resuming in some degree the earlier rigid hemiplegic posture (fig. 2*c*). I shall later return to the significance of these postures, for they are a key to much that is obscure in the pathophysiology of the basal ganglia.

Huntington's Chorea

It is not necessary here to outline the characteristics of Huntington's chorea except to point out some distinctive



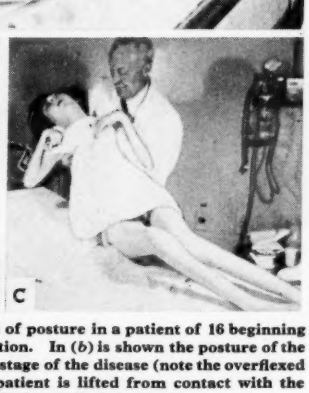
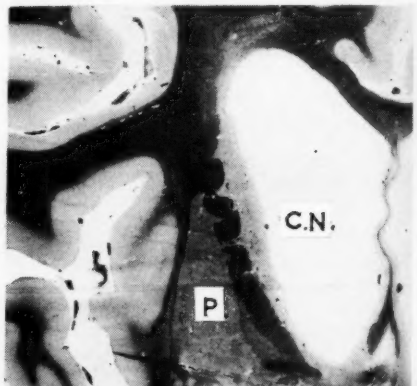


Fig. 2—To show (*a*) the early abnormalities of posture in a patient of 16 beginning to show signs of hepatolenticular degeneration. In (*b*) is shown the posture of the same patient 4 years later, in an advanced stage of the disease (note the overflexed wrists, with extended fingers). If the patient is lifted from contact with the surface of the bed (*c*) all limbs stiffen and the lower limbs extend.



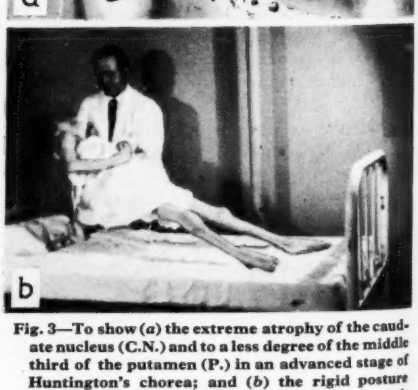


Fig. 3—To show (*a*) the extreme atrophy of the caudate nucleus (C.N.) and to a less degree of the middle third of the putamen (P.) in an advanced stage of Huntington's chorea; and (*b*) the rigid posture when such a choreic patient is raised from the bed.

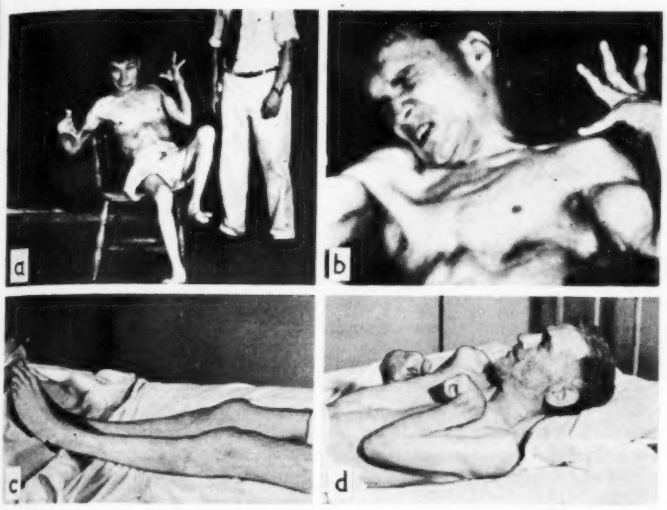


Fig. 4—To show the " mobile spasm " with athetosis of hands and lips (*a* and *b*) in double athetosis. In the terminal stage a rigid posture of extension of the lower limbs (*c*) and flexion of the upper limbs (*d*) replaces the " mobile spasm ".

features of the involuntary movements and postures. The movements are essentially labile and haphazard in distribution. I have described elsewhere (Denny-Brown 1950) how the movements of the hands and arms gradually assume the swings of posture seen in athetosis, though at a faster rate. This is first seen in walking. The movements of the lips and jaw gradually develop the wider amplitude, with associated incoordinate action of the platysma muscles, that is a feature of double athetosis. For a long time the limbs are hypotonic, but the posture gradually becomes more stooped, and in late stages of the disease rigidity may appear, with more characteristic slower athetoid movements. The posture is then a rigid hemiplegic attitude, which is greatly intensified by raising the patient from contact with any surface (fig. 3). The arms are strongly flexed, and the legs and ankles stiffly extended. This posture is the same as that mentioned as a late stage of Wilson's disease.

When the onset is early, rigidity may be the most prominent symptom (Kehrer 1928). There is then close resemblance to parkinsonism, including pill-rolling tremor of the fingers (Fleischhacker 1924, Josephy 1936). In a few patients unmistakable parkinsonism develops later in life (Chandler et al. 1960), though the lower limbs are, in my experience, more often extended stiffly than flexed in the usual parkinsonian posture. Besides atrophy of the frontal cortex, shrinkage of the caudate nuclei is almost universally present, together with some loss of cells in the middle third of the putamen (Marie and Lhermitte 1914, Dunlap 1927), with pallor of the corticostriate and striopallidal systems (fig. 3). A condition of fibrous scarring of the putamen, called " status fibrosus " by the Vogts (1920) and Jakob (1923), has been found in the cases presenting rigidity (Bielschowsky 1919, Terplan 1924, Freund 1925). In some cases the degeneration extends to the globus pallidus and subthalamic nuclei. The extrapyramidal manifestations of Huntington's chorea, as with Wilson's disease, are seen to form a spectrum of types of movement disorder in relation to an evolving pathology, ranging from early myoclonic twitchings in some cases to torsion spasm and rigidity, and, more rarely, parkinsonism. The most characteristic choreic movements reflect only the usual early affection of caudate nucleus and frontal cortex.

Double Athetosis

The case selected by Vogt (1911) as the prototype of striatal disease presented an unusually well-localised marbled scar in the outer segment of the putamen on both sides. The clinical symptoms are usually a bilateral labile type of athetosis affecting all parts, but particularly the hands, mouth, and neck, and present from the first year of life. The condition is now well recognised, and is usually called " double athetosis " (fig. 4*a* and *b*). The scar tissue appears to be a static inactive process. Many follow Courville (1953) in attributing it to anoxia at birth. In several cases there has been similar scarring of the cerebral cortex (Alexander 1942), but there is no doubt that the lesion in the putamen can occur alone, and in association with a bilateral mobile type of athetosis present from soon after birth. In many cases rigidity of the limbs appears later, gradually slowing the athetosis to " mobile spasm," and leading ultimately to intense flexion of the upper limbs and extension of the lower limbs (fig. 4*c* and *d*). When rigidity has complicated athetosis in this way the scarring of the putamen is usually more extensive, but few cases have been analysed from this point of view.

Dystonia Musculorum Deformans

In its progressive form, dystonia is the most striking and grotesque of all neurological disorders. The progressive small spasms of flexion of a lower limb, or alternatively of torticollis, that are usually the first manifestations in early childhood, first appear as additions to movements such as walking. Only when continuous maintenance of the abnormal posture occurs is the dystonic condition recognised. Though I have earlier indicated the essentially athetoid character of the beginning of the disorder (Denny-Brown 1945), its relation to athetosis is still overlooked, for the first signs are spasms in willed movement rather than involuntary movements. As the disorder progresses new intermittent elements of athetoid spasm make their appearance; they are set up, like the first, by any stimulation or attempted movement, but they gradually become more constant. The cumulative steady spasm of flexion of proximal joints has added to it extension of the fingers and toes, retraction of the jaw, and lordosis. The later addition of intermittent spasm in antagonistic muscles, followed by continued contraction in antagonists, leads to the great deformity. Unless there is accompanying spasticity, the asymmetrical postures and movements can be profoundly changed by altering the areas of body in contact with the bed or examining table. If the patient is lifted free from all contact with the body surface, save for support under the axilla, the upper limbs flex and the lower limbs extend in hemiplegic posture (fig. 5). If movements have been in progress they cease when the child is suspended. When the patient lies on one side the lowermost limbs extend and the uppermost flex. These changes indicate that reflex effects from contact between the body and supporting surface are important factors in the production of the abnormal movements and postures.

Fig. 5—Dystonia musculorum deformans. To show the abnormal attitudes and their modification by suspending the patient and by lying on a flat surface.
(Photographed at Wrentham State School, with kind permission of Dr. Carl Quinn.)

Dystonia is a symptom complex that has many causes, but the irregular and grotesque progressive deformity described above, with cumulative development in one body part after another, has not been clearly correlated with pathological processes other than status marmoratus, which closely resembles the lesion of double athetosis, but usually involves the thalamus and cerebral cortex in addition to the putamen. Thomalla (1918), Wimmer (1921), Jakob (1932), and others have reported the lesions of Wilson's disease in relation to relatively symmetrical dystonia. Lethargic encephalitis was undoubtedly the cause of many cases of asymmetrical dystonia of partial and arrested types. The cases of Cassirer (1929), Jakob (1923), Marinesco and Nicolesco (1929) and Laruelle and van Bogaert (1929) showed milder changes in the form of pallor of the globus pallidus and cell loss in the putamen. There is some possibility that such cases are postencephalitic.

More Diffuse Lesions of the Basal Ganglia

From the great variety of diffuse degenerative processes that affect the basal ganglia, I have singled out Wilson's disease, Huntington's chorea, and status marmoratus as examples where rigid " dystonic " states can be related to relatively localised destruction of the putamen. Before turning to the problem of parkinsonism, we should briefly review some of the other types of diffuse pathology that affect the basal ganglia. These are all rare and obscure syndromes, and I shall here only comment on the type of movement disorder in relation to anatomical lesion.

Calcification of the basal ganglia (Fahr's syndrome) is an affection of the walls of small blood-vessels of these organs that may reach considerable intensity, even to the degree of visibility in skull X-rays (Fahr 1930), without neurological symptoms. There may or may not be associated hypoparathyroidism (Sugar 1953). The neurological disorder that eventually appears is a generalised rigidity, most commonly beginning in the lower limbs (Fritsche 1935, Chavany et al. 1949), with or without athetoid movements. Parkinsonism developed in middle life in the patients of Jakob (1923) and of Alexander and Tucker (1949). The calcification in such cases begins on the border between the putamen and globus pallidus. In a remarkable familial case of my colleague, Dr. Paul Yakovlev, such calcification resulted in dysarthria with intense ridigity of all limbs in flexion.

Similar flexion postures eventually result from diffuse *lipidosis* of the juvenile type (Sjögren 1931, Watson and Denny-Brown 1953). Similarly in the *Hallervorden-Spatz syndrome*, where deposits of iron-containing pigment accumulate in the globus pallidus, thalamus, substantia nigra, and dentate nuclei, there results a diffuse rigidity of the limbs in flexion, with or without athetosis. It is also notable that, both in this syndrome and in lipidosis, there is a liability to sudden jerks of the limbs in flexion (myoclonus) as a prelude to the eventual postural change.

The Enigma of Parkinsonism

The most common of extrapyramidal syndromes—parkinsonism—presents the most difficult problems in this whole group of diseases. There is still no agreement as to the essential change in anatomical structure:

The pallor of the ansa lenticularis and related efferent pathways of the pallidum, and the progressive loss of cells in the globus pallidus and, to a less extent, the striatum, described by Jelgersma (1908) and by Lewy (1913), have been found by many others (Lhermitte and Cornil 1921b, Bielschowsky 1922, Jakob 1923, Foix and Nicolesco 1925). In 1919 Trétiakoff drew attention to some loss of cells in the substantia nigra in paralysis agitans, as well as to the severe destruction of this nucleus in postencephalitic parkinsonism. This feature of the disease has gained greater emphasis in the past twenty-five years (Hassler 1937a and b, Benda and Cobb 1942). Greenfield and Bosanquet (1953) have confirmed scattered cellular changes in the locus cœruleus of the pontine tegmentum, as well as in the substantia nigra, found earlier by Foix and Nicolesco, and by Hassler. In his posthumous textbook on neuropathology, Greenfield (1958) states that the lesions in the globus pallidus, though constant and sometimes severe, are " essentially those of senility ".

Our own pathological material in the Boston City Hospital consists of 21 cases; 5 of them are clearly postencephalitic, 7 have atherosclerotic lacunar lesions in the putamen, and 9 could be clearly calssified clinically and pathologically as idiopathic paralysis agitans. Only 2 cases had been subjected to serial whole-brain sections, but multiple sections of the basal ganglia and midbrain of all the others were available for study.

All cases of parkinsonism exhibited some degree of pallor of the globus pallidus and the ansa lenticularis, in sections stained for myelin sheaths. The corresponding loss of nerve-fibres was more impressive than loss of nerve-cells. In *paralysis agitans* the pallor was usually uneven, and foci of loss or thinning of myelin sheaths were particularly evident in the outer pallidum near the external lamina. In Nissl sections such foci were represented by small inconspicuous areas of loss of cells from the otherwise evenly scattered pattern of pallidal cells. In 2 cases small concretions were present in the ground substance, not directly related to the foci. Gliosis was mild in degree. In no case was there any evident disease of blood-vessels, other than some mild siderosis in 2 cases (a change commonly found in the globus pallidus after middle life). In one patient who died after a head injury all striopallidal and corticopallidal fibres stained very poorly compared with the pallidal efferents in the ansa lenticularis. In the most severely affected cases all the pallidal cells were shrunken and stained poorly, and their lipid content appeared to be increased in relation to their size. In 5 cases, and doubtfully in 2, the substantia nigra showed the small lesions described by Hassler. No cell or fibre lesion was found in the nigra in 2 cases.

The lesion of the globus pallidus is described by Bielschowsky (1922), and in detail by Foix and Nicolesco (1923, 1925), who called it " paravascular degeneration ". It was regarded as the first stage of a change that later leads to more evident loss of tissue elements (*état précriblé*), and later still to pericapillary destruction of tissue (*état criblé*). It should be emphasised, however, that in paralysis agitans with paravascular degeneration no evidence of change in the walls of blood-vessels can usually be found. If siderosis is present it must be an independent abnormality, for it can be severe in degree without producing paravascular degeneration. The pattern of tissue damage reflects some peculiarity in the permeability of the smallest blood-vessels in this area, and is common in the earliest stage of some of the metabolic diseases affecting the basal ganglia.

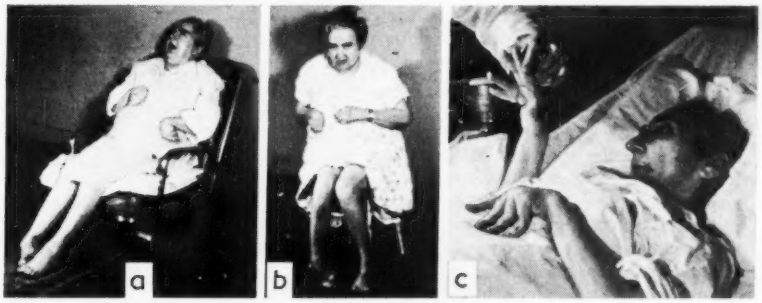


Fig. 6—Terminal stages of paralysis agitans, to show flexion dystonia.

When *atherosclerosis* has affected the vessels of the basal ganglia, lesions of the putamen are more obvious than those of the globus pallidus. Lacunes of softening appear in the putamen surrounded by foci of *état criblé*. The clinical state is then most commonly that of pseudobulbar paralysis, with or without damage to the internal capsule and cerebral white matter. In 2 of our cases with typical parkinsonian tremor and attitude, mild *criblé* lesions were limited to the internal part of the putamen and outer globus pallidus. Only associated atherosclerosis of the arterioles, and the presence of the *criblé* state in the putamen, then differentiate arteriosclerotic parkinsonism of this type from what we would call true paralysis agitans. The pericapillary degeneration itself is more severe but otherwise closely resembles " paravascular degeneration ". There may be small foci of similar paravascular degeneration in the substantia nigra, but these are not necessarily present. Paravascular degeneration, I believe, is not directly the result of atherosclerosis but is worsened in extent and degree by its presence. The evidence for this will presented elsewhere. The occasional cell inclusions that have been noted by Lewy (1923), Hassler (1937a), and Greenfield and Bosanquet (1953) in the substantia nigra have been found in the Boston City Hospital in all types of case. I am not convinced that they are a primary or specific change.

In my monograph in 1945 I made a sharp distinction between true paralysis agitans and arteriosclerotic parkinsonism. With greater experience I have to admit that this distinction is not absolute. There is every degree of transition. At one end of the scale one can recognise a slowly progressive gentle tremor at rest, with mild rigidity, that may begin in the fifth decade, with slight paravascular changes limited to the globus pallidus. At the other extreme the marked rigidity and fixed hemiplegic posture of the pseudobulbar type is related to the " lacunar " state, with multiple small infarcts of the putamen. Between lies every conceivable relative proportion of tremor and rigidity. Thus arteriosclerotic parkinsonism may begin with rigidity, tonic grasp, and tonic foot response, with very little tremor. In this type the putamen appears to be invariably damaged, and is perhaps first affected. Yet rigidity can also occur with pallidal lesions. A patient of mine, an 81-year-old man who had first developed typical parkinsonian rigidity and tremor twenty-one days before death, presented recent partial infarction (circumscribed pallor) of the globus pallidus on both sides. There was no change in the substantia nigra. Lhermitte and Cornil (1921a) cited a similar case.

The symptomatology of paralysis agitans consists of the well-known tremor and rigidity. In the tremor the opposed thumb beats against the first finger, and is associated with tremor of the lips and tongue before other parts. The soft yielding plastic rigidity of paralysis agitans appears first in the flexors of the upper limbs, and is associated with delay in initiation of movement, though the relative degrees of bradykinesia and objective rigidity are greatly variable. Seldom is it emphasised that in typical paralysis agitans the rigidity is invariably associated with change in posture, its preponderance in the flexor groups gradually leading to the stooped posture with flexed limbs, fixed facies with staring eyes, and open mouth, by which parkinsonism can be recognised in a photograph. It is important also to emphasise that in the natural course of the disease the postural change gradually worsens until in a terminal stage all the limbs are drawn into a fixed attitude of general flexion (fig. 6). The wrists are then strongly flexed and pronated, the fingers are extended, and the ankles are plantar flexed. Attempted displacement of any part away from this attitude then meets a mounting resistance, and the part rapidly returns to its resting attitude. This terminal loss of plasticity is associated with great lessening or loss of the tremor. Speech is also lost or reduced to a mumble.

Studies of arteriosclerotic parkinsonism indicate that the coarser the lesions of the external segment of the globus pallidus the more rapid has been the development of dystonia, with correspondingly less evident tremor. If the putamen is involved tremor may not occur, and the rigidity is then not only more intense but also involves the extensors of the lower limbs and the flexors of the upper limbs (hemiplegic distribution). The pattern of rigidity as well as its intensity reflect the more lateral and lacunar lesions.

In *postencephalitic parkinsonism*, though the same tremor may be present, it is more often damped or abolished by an intense asymmetrical rigidity. The rigidity passes more rapidly into the fixed attitudes of dystonia, leading to torticollis, scoliosis, and grotesque postures of the limbs. On the side on which dystonia was absent or delayed in appearance, the tremor tends to be more violent and more extensive than in paralysis agitans. In addition various forced movements and compulsions, of which the oculogyric crises are the best known, are peculiar to the postencephalitic state. Like others, we at Boston have found a severe destruction of the substantia nigra in all

cases, but we have also found a diffuse pallor of the fibre systems of the globus pallidus. Obvious nerve-cell changes in the globus pallidus or striatum are seldom found, but small foci of lesser change are common. More important, we have often found loss of the small thinly medullated fibres entering the external putamen from the external capsule, and the external lamina of the globus pallidus from the internal capsule, with or without paucity of striopallidal fibres. There is corresponding gliosis. This inconspicuous change is of great significance in relation to the prominence of symptoms of corticostriate and corticopallidal disorder, and I shall return to it in my second lecture. In the acute stages of lethargic encephalitis destruction of the substantia nigra was commonly found in patients without parkinsonism (Meyer 1923, Holzer 1926). If 75% of the substantia nigra is destroyed in most cases of postencephalitic parkinsonism, this still fails to account for the varied and complex disorders of motor function of that disease, and their delay in appearance. Still less is the similar symptomatology in paralysis agitans explained by the inconstant meagre changes in the substantia nigra and locus cœruleus in that disease.

Focal Lesions of the Basal Ganglia

The natural history of diseases that commonly affect the basal ganglia of the brain has been outlined in order to draw attention to their general tendency to produce involuntary movements that progress slowly to states of rigid maintenance of abnormal attitude. We shall now turn to the effects of acute destructive lesions, which, by contrast, produce striking disorders of attitude from their beginning.

Necrosis of the Striatum (Putamen and Caudate Nuclei)

Bilateral symmetrical necrosis of the caudate nucleus and putamen has been found in conditions such as death from status epilepticus in children, when anoxic damage to small vessels is presumably the primary mechanism:

Marinesco and Draganesco (1929) describe this condition after convulsions in a child aged 4½ years, who survived to the age of 6. There was patchy laminar necrosis of the cerebral cortex, and only mild degenerative changes were found in the globus pallidus. Until death the child lay in an unresponsive state without making purposeful movements. There was complete absence of speech, and swallowing was difficult. At first the limbs were extremely rigid in flexion, but they would extend with changes in posture, and athetoid movements were present. Later rigidity was less evident when the child lay on a surface, though all the limbs were semiflexed, the wrists pronated, the fingers flexed, the ankles extended, and the toes plantar flexed. When the child was suspended in air, all the limbs became intensely rigid, the arms flexed, the hands clenched, the lower limbs extended, the ankles inverted, and the toes flexed. This posture would persist as long as the child was suspended. This phenomenon of the appearance of rigidity when the patient is lifted from a surface is commonly called " the Foerster syndrome ". Foerster (1909), however, described only the atonic type of cerebrocerebellar diplegia, and the extension of the limbs when suspended appears to have been first described by Batten and von Wyss (1915).

Hawke and Donohue (1951) described, in a 13-year-old child, a similar complete bilateral necrosis of the whole corpus striatum, caudate, putamen, and globus pallidus, which occurred during a febrile illness complicating otitis media, without any known episode of anoxia. During two months of survival the child did not speak or respond to commands. The eyes would follow the movements of another person, and even moving objects, late in the survival period. The muscles were at first hypotonic, but they gradually became stiff in flexion, particularly during passive movement. Occasional myoclonic twitching of muscles was observed. The remarkable phenomenon of rigidity when suspended is not mentioned by these workers. Similar cases have been reported by Verhaart (1938).

Complete clinical and anatomical studies of cases of unilateral destruction of the putamen and caudate nucleus are equally rare. I cannot here discuss in detail such a case in the collection of my colleague Dr. Yakovlev; suffice it to say that for the last ten years, before death at the age of 25, the patient had presented a dystonic contracture of the right arm in flexion and the right leg in extension, with consistent flexor plantar responses. There was a severe spastic dysarthria. Mobile athetoid spasm of the hand had preceded the dystonic attitude of extended fingers, and flexed wrist and elbow. Steck (1921) reported a similar case, though the dystonia was not fully described.

When bilateral partial cystic infarction of the putamen has occurred without damage to the internal capsule, the clinical condition has been that of pseudobulbar palsy (as first described by Richard Bright 1831). The pseudobulbar state resulting from Wilson's disease, and the condition resulting from manganese poisoning (Peñalver 1955, Berry and Bidwai 1959), have obvious features in common.

Necrosis of the Globus Pallidus

One of the most striking lesions of the basal ganglia is the symmetrical necrosis of the globus pallidus found in patients who have had an episode of coma as a result of inhalation of coal gas, or carbon monoxide, or occasionally nitrous oxide, and rarely in those who have had other types of asphyxic anoxia. It can also follow intoxication by carbon disulphide (Richter 1945):

The patient commonly recovers from the initial coma, and he may be discharged from hospital apparently completely relieved, or with only slight mental confusion. After one to three weeks, he may then relapse into coma a second time, and succumb in that state. Most often the delayed relapse presents as the onset of an akinetic mute state, with rigidity. In other cases the relapse takes the form of renewed confusion in which elements of visual agnosia and catatonic postures are prominent, presumably resulting from lesions of cerebral white matter. In a few cases a mild parkinsonian rigidity makes its appearance within six weeks of recovery from the initial coma.

I need not here discuss the many interesting aspects of the neuropathology, which has recently been reviewed by Meyer (1958), whose earlier papers are among the most authoritative. Widespread patchy areas of cortical ischæmic damage may occur. Their presence is to be suspected whenever mental confusion is persistent. The lesion that concerns us here more particularly is necrosis of the globus pallidus. It is commonly found when death has occurred soon after exposure, without recovery from coma, and it is usually bilateral and approximately symmetrical. Some part of the globus pallidus, usually the most anterior part of the internal segment, is the site of a hæmorrhagic softening, commonly occupying only a small part (10 to 20%) of the nucleus. There is usually no incrustation of the vessels in this early stage. The necrosis is clearly secondary to vascular damage.

Where death has occurred after a delayed relapse, with onset of akinesia and rigidity, the infarct is usually larger, and it may involve the external segment or even portions of the putamen. An associated lesion of the substantia nigra has been reported (Hiller 1924) but is very rarely found. In a few such cases evidence of cortical damage is very slight, and white-matter lesions have been absent.

Of 2 such cases followed closely in life, 1 showed an unvarying akinetic state for six months:

This 58-year-old man was found in coma in a small unven-

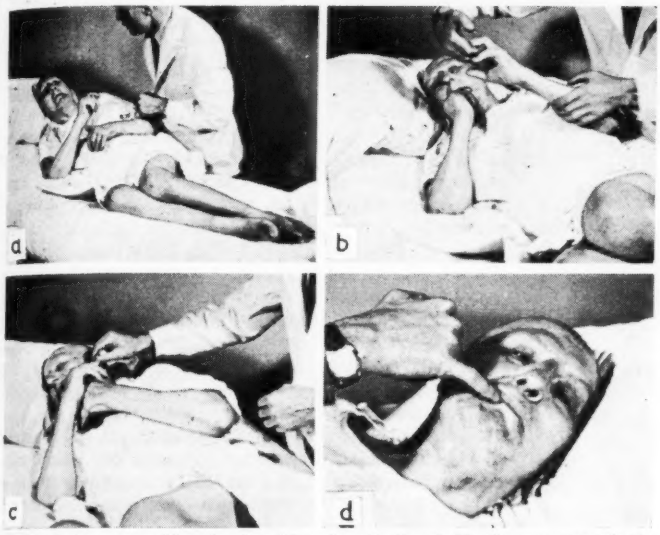


Fig. 7—Carbon-monoxide poisoning: (*a*) to show the flexed akinetic mute state, (*b*) the absence of grasp response, (*c*) the small response to pinprick on the face, and (*d*) tight closure of the mouth when lips were touched.

tilated hut, with a burnt-out brazier fire, without chimney. He lay unreflexic for a day, but then made a rapid recovery. Eight days later he was able to speak, to read a newspaper, and to travel from Florida to Boston. On the ninth day he was found to be very drowsy, and he rapidly lapsed into an unresponsive state, with arms and legs moderately rigid in semiflexion. His eyes were open, and they occasionally followed the movements of the examiner. He slowly scratched the face if pricked with a pin, but he gave no other reaction. The deep-tendon reflexes were present but not increased. Both plantar responses were extensor. The face was expressionless. Swallowing was possible only if fluid was introduced far back into the mouth. Any attempt to open the lips or mouth passively met increasing resistance. The limbs were held continuously in a semiflexed posture, the wrists were flexed, and the ankles extended. Because of mild plastic rigidity, they resisted attempts to extend them passively. The fingers were extended and were not used, except for a feeble brushing movement at a noxious stimulus to the face. There was no grasp response to a light stimulus, but, occasionally, after heavy stroking, a feeble grasp was obtained. Such responses are illustrated in fig. 7 from another patient, who survived in an identical state for many months, but in whom necropsy was not obtained.

In the first patient examination of the brain showed the characteristic lesions of the globus pallidus. There was no lesion of the substantia nigra, or thalamus, or other part of the extrapyramidal system. The cortex was virtually unaffected, but some patchy lesions in the frontal white matter of the orbital cortex were found on both sides, with a smaller lesion in the deep parietotemporal white matter. In this case vascular lesions of two different stages were apparent, supporting the hypothesis that the lesion had in fact enlarged after the latent interval. The occluded vessels were calcified in the area of more recent extension of softening.

In general small pallidal lesions have not been associated with extrapyramidal signs other than slowness in initiation of movement. The most intense akinesia and rigidity has followed large lesions. Where rigidity in flexion has followed after a long interval, I suspect that the lesion has enlarged because of delayed vascular changes, even after as long as seven years (Alexander 1942); and even forty-nine years in the report of Yakovlev (1944).

Focal Subthalamic Lesions

Discussion of the involuntary movements of *hemiballismus* resulting from lesions in the subthalamic nucleus will have to be omitted, except to emphasise that the characteristic movement involves a rotary element at proximal joints. This rotary element also appears in the posthemiplegic chorea associated with some types of thalamic lesion, and in the " midbrain " tremor so well described by Holmes (1904). When progressive lesions affect the general region of the midbrain tegmentum, rigid extension and internal rotation of all limbs eventually appears. This is the most common type of " decerebrate rigidity " encountered in man. Cathala (1922) has described a unilateral example resulting from tumour of the tectal region.

General Conclusions

In this necessarily abbreviated account of the general aspects of the symptomatology of diseases of the basal ganglia I have emphasised the diffuse nature of the pathology of such diseases, and their general tendency to produce involuntary movements that gradually make transition to abnormal postures. These two features are of special importance, for one of the most baffling aspects of these syndromes has been the inability of the physiologist to reproduce them by surgical or electrolytic lesions. It has not been appreciated that focal necrotic lesions of the putamen and globus pallidus can in man produce the terminal states that are seldom reached by degenerative diseases of the same structures. In particular I would stress the akinetic mute state of general flexion of all limbs, with pronated wrists and extended fingers, that is characteristic of severe destruction of the globus pallidus (" pallidal syndrome "). In milder degrees there is associated tremor of parkinsonian type. In contrast the more rigid flexion of upper limbs and extension of the lower limbs, greatly intensified by suspending the patient free of contact with body surface, is characteristic of destruction of the putamen and caudate nucleus (" striatal syndrome "). Lesser degrees of this disorder are characterised by athetosis and " mobile spasm ". With these two basic postural changes in mind, their physiological meaning, and the significance of the disorders of movement that are associated with them, may be approached.

(The references will appear at the end of the second lecture.)

". . . The more efficient society becomes at rapidly modifying our environment and our ways of life, the more unpredictable are the responses of man to the new conditions of his own making. . . . In order to meet its professional responsibilities, medicine must add to its preoccupation with di ease the study of the responses of normal man to the rapidly changing environment. It must supplement the knowledge of pathology with a new science which might be called biological technology. At least, this is the conviction which has led me, a bacteriologist, to focus my thoughts increasingly on the factors, external and internal, which condition the response of man to the microbes which are an ubiquitous part of his environment." —RENÉ J. DUBOS, *J. Amer. med. Ass.* 1960, **174**, 505.

HYPERSENSITIVITY TO MILK AND SUDDEN DEATH IN INFANCY

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IN a review of the possible causes of sudden death in infancy, Barrett (1954) suggested that of such cases "perhaps the majority are due to the inhalation of regurgitated food into the lungs". The inhaled food might not cause death by directly obstructing the air-passages: an amount of milk too small to cause immediate asphyxia might excite an inflammatory reaction accompanied by pulmonary œdema, or the absorption of undue amounts of milk derivatives into the blood-stream might cause a state of shock.

Such effects of inhaled food or vomit, if they occur, might be due either to an inherent toxicity of the inhaled material when it enters the body by this abnormal route, or to an anaphylactic type of reaction resulting from antigenic sensitisation.

We present some experimental evidence which suggests that the second, but not the first, of these two mechanisms is indeed a possible cause of sudden death in infancy. The hypothesis is that some infants may be in a hypersensitive state from the development of antibodies to the proteins of milk absorbed from the alimentary tract. Infants often regurgitate stomach contents while asleep, and should some of this material be aspirated into the respiratory tract of an infant which has become hypersensitive, the result might be fatal.

There is no doubt that most infants fed on cow's milk develop antibodies to the proteins of the milk. Gunther, Aschaffenburg, Matthews, Parish, and Coombs (1960) using a sensitive technique—the coated tanned red-cell test of Boyden (1951)—showed milk antibodies in normal children aged 7–97 weeks in a titre up to 1000 with a modal distribution around a titre of 64.

There thus seems to be ample evidence that the majority of infants are immunised to some degree or other to the proteins of cow's milk, and the possibility exists that these or other types of antibody may sensitise the tissues of the infants. Anderson and Schloss (1923) showed that in infants with some types of nutritional disorders, milk proteins were absorbed via the alimentary tract and that subsequently precipitins to milk protein could be shown in the infants' sera, and these antibodies could sensitise guineapigs passively to anaphylaxis. According to Clein (1958), up to 6% of infants during the first few months of their lives are allergic to cow's milk.

Parish, Barrett, and Coombs (1960) showed that administration of milk over the glottis into the larynx of unsensitised conscious guineapigs was for all intents and purposes without clinical effect. On the other hand, a small amount of milk dropped into the larynx of sensitised guineapigs resulted in a characteristic anaphylactic reaction often leading to death. The reaction itself and the pathological findings in such animals were those of frank anaphylaxis and did not resemble those seen in human cot-death cases. If, however, the guineapigs were lightly anæsthetised—an experimental condition used to simulate the condition of the sleeping child—milk introduced into the larynx had quite a different effect. In the unsensitised guineapigs there was no untoward effect, and even in the sensitised animals there was a complete absence of the usual features of anaphylaxis seen in a conscious animal. Very soon after introducing the milk preparations into the larynx of an anæsthetised sensitised guineapig, the animal stopped breathing without any signs of struggle. Death sometimes occurred immediately, but the majority of animals took deep breaths at 10–30-second intervals for a variable period. Death was preceded by a short period of more rapid breathing, each respiratory effort being shallower than the preceding one, until, with a final nose-twitching, the animal died. Others lingered for 20–60 minutes before death took place, or normal respiration was gradually resumed. This sequence of events became recognised as characteristic, and was reproducible on challenge of all the anæsthetised sensitised animals. The pathological findings in the animals which died resembled those in human cot-death cases.

In the present paper we have tried to relate our experimental results more directly to the condition in man. (1) Sera from actual cases of cot death have been examined for their level of milk antibodies, as shown by the coated tanned red-cell test, in order to see if the distribution of levels is higher, as would be expected, than in randomly selected infants of comparable age. (2) To test our hypothesis that the aspirated milk proteins originate as a regurgitation from the stomach, experiments have been performed on anæsthetised sensitised guineapigs in which the stomach contents recovered from cases of cot death were introduced into the respiratory tract. Only stomach contents from infants known to have been bottle-fed at the time of death were used. (3) Experiments have been performed to see if the individual milk proteins can produce a lethal effect. (4) The pathological findings in guineapigs killed in this way are compared with those in cases of human cot death.

Materials and Methods

These have been described in detail in two previous papers (Parish et al. 1960, Gunther et al. 1960).

Milk and Milk Proteins

As National dried milk powder is the product given to the majority of bottle-fed infants, it was employed as the source of milk proteins in our previous studies. In the present work this product was again used as the sensitising antigen and the soluble proteins of the reconstituted powder used to coat the tannic-acid-treated red cells in the serological tests for milk antibodies.

The isolated proteins of cow's milk—namely, casein, α-lactalbumin, and β-lactoglobulin—were prepared as described by Gunther et al. (1960) and were kindly supplied by Dr. R. Aschaffenburg.

Testing Sera for Antibodies

The method was basically the coated tanned red-cell technique of Boyden modified as described by Gunther et al. (1960). The tanned red-cells were coated by exposing them to a 0·5% solution of protein antigen.

Sensitisation of Guineapigs and Challenge

The guineapigs each received one intraperitoneal injection

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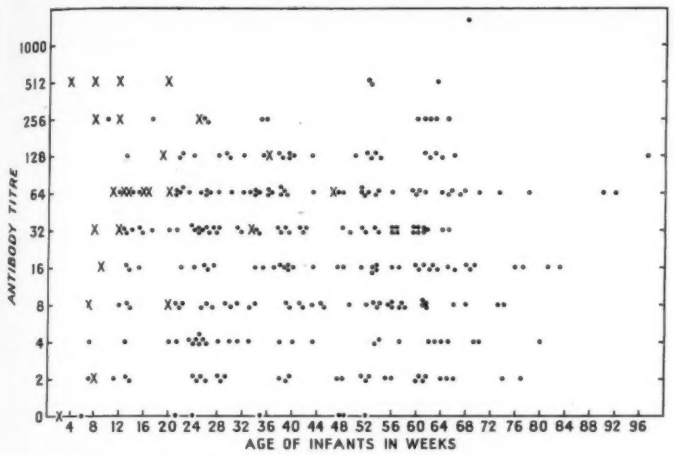

Fig. 1—Titres of serum-antibody to cow's milk proteins at various ages in 24 "cot-death" cases (X) and in 286 normal infants (•).

A strict comparison of the two categories is not possible for the reasons stated in the text.

of 1 ml. reconstituted milk powder 2% w/v. The inoculum consisted of the soluble and insoluble material.

In experiments with human stomach-contents the animals were challenged on the 18th day after injection. In experiments with milk proteins they were challenged on the 69th day.

Anæsthesia

Pentobarbitone ('Nembutal') was used as the anæsthetic in a dose of 0·01 ml. per 20 g. body-weight given intraperitoneally. The depth of anæsthesia was such that the corneal reflex was very weak or just absent and the pedal reflex still present. This was usually achieved in 15 minutes after injecting the pentobarbitone.

Challenge via the respiratory tract.—This was designed to mimic, as closely as possible, the accidental inhalation of regurgitated stomach contents by the sleeping infant. The method has been fully described and illustrated by Parish et al. (1960). With the aid of a gag and an illuminated nasal speculum, the mouth was opened and the entrance to the pharynx exposed. While the tongue was depressed by a thin metal spatula, the milk or other challenging antigen was introduced over the glottis from a specially shaped blunt needle attached to a syringe. When the animal inspired through the mouth it was possible to see the epiglottis which was the guide to the site of injection. With practice it was possible to deposit the milk drop by drop over the glottis so that it was inhaled even when the larynx was invisible to the operator. This procedure caused the minimum amount of damage to the respiratory tract.

Experimental Study

Serum Antibody Levels

Using coated tanned red cells Gunther et al. (1960) tested the sera of 286 normal children aged 7–97 weeks (fig. 1). Nearly all the sera contained measurable antibody to cow's milk proteins. In distribution the mode fell around a titre of 64. Approximately 4% had a titre of 256, 1% a titre of 512, and one serum had a titre of 1000. The plot of serum titre against the age in weeks of the child is shown in fig. 1.

We have now tested sera from 24 cases of cot death for the titre of antibodies to cow's milk. Only those cases of sudden death were included which, on the pathologist's report, could be considered as "cot-death" cases. These infants were known to have been bottle-fed at the time of death, and milk was found in their stomachs at post mortem.

The serum titres of antibody to cow's milk in the cot-death cases are also shown in fig. 1 where the distribution can be seen in relation to that found in normal infants.

The number of cases available so far is not sufficient for a final assessment, nor is the mode of selection in the two categories appropriate for a strict comparison between the serum levels in normal infants and in the cot-death cases. In the first place approximately 32% of the normal infants were known to be mainly breast-fed at 6 weeks of age, while the cot-death cases studied were all bottle-fed at the time of death. Moreover, the blood from normal infants was collected under ideal conditions and the sera frozen to −15°C within 5 hours of bleeding, while the blood from cot-death cases was obtained post mortem and often had considerable precipitates which had to be centrifuged out before testing. However the high titres found in the sera of the majority of cot-death cases are in keeping with the possibility that, had these infants aspirated milk into their respiratory tracts, a lethal hypersensitivity reaction, as seen experimentally in guinea-pigs, might have occurred.

We are not suggesting that the level of serum antibody is necessarily a measure of the degree of sensitivity, although for the type of anaphylactic reaction envisaged this cannot be excluded. It does indicate, however, that the infants have received a considerable antigenic stimulation with cow's milk and are, for this reason, potentially sensitised to these proteins.

Effect of Stomach Contents on Sensitised Guineapigs

In our previous experiments (Parish et al. 1960) National dried milk was used as the material for challenge. In the present paper we report a similar experiment but the material used was stomach contents from actual cot-death cases in which the infant's last feed had been from the bottle. This was used because, in the hypothesis we put forward, we believe regurgitated stomach contents are the source of the aspirated material initiating the lethal reaction.

In this experiment both sensitised and unsensitised (control) guineapigs were lightly anæsthetised with an intraperitoneal injection of pentobarbitone. Approximately 15 minutes later, when the desired state of anæsthesia had been reached, 0·25 ml. of a 1/2 dilution of stomach contents (0·125 ml. of the original contents) was introduced into the larynx. Stomach contents from 4 cases of cot death were used. The tenaciousness of this material necessitated its dilution with an equal volume of saline to avoid mechanical obstruction of the respiratory tract of the guineapig, which is, of course, much narrower than that of the human infant. The stomach contents were obtained from dead infants aged 2, 4, 8, and 22 weeks. The larger lumps found in the stomach of the oldest child were first broken down in a Griffith grinder.

TABLE I—CLINICAL EFFECTS OF INHALING STOMACH CONTENTS FROM HUMAN COT-DEATH CASES BY NORMAL AND BY PREVIOUSLY SENSITISED GUINEA-PIGS LIGHTLY ANÆSTHETISED TO SIMULATE SLEEP

Challenge with stomach contents of dead infant	Dose of diluted stomach contents	Sensitised guineapigs		Unsensitised guineapigs	
		Reactions	Deaths	Reactions	Deaths
A, aged 2 weeks	0·25 ml.	D D D D + + +	4/5	+ − − − −	0/5
B, aged 4 weeks	0·25 ml.	D D D + + −	3/5	− − − − −	0/5
C, aged 8 weeks	0·25 ml.	D D D D	4/4	− − − −	0/4
D, aged 22 weeks	0·25 ml.	D D D D + +	4/5	+ + − * −	0/5

Scale of severity of clinical effects:
D = death.
+ + + = severe respiratory embarrassment just insufficient to be fatal.
+ + = definite clinical disturbance but not severe.
+ = one or two signs of respiratory embarrassment but always mild.
− = no response.

In the unsensitised guineapigs no deaths, and in the great majority of cases no effects, were observed. On the other hand most of the sensitised animals exhibited the syndrome already described and died silently, without any struggle, and in a very short time. Three animals recovered after a protracted period during which there were long spells of apnœa interrupted only by occasional weak gasps. One of the sensitised animals was apparently unaffected. The results are summarised in table I.

Effect of Milk Proteins on Sensitised Guineapigs

In our earlier report (Parish et al. 1960) we recorded the level of milk antibodies and the clinical sensitivity to challenge with milk at 17, 38, 64, and 92 days after a single sensitising injection. Although in some animals the level of serum-antibody appeared to fall with the passage of time the animals were as sensitive clinically to the aspiration of milk on the 92nd day as they were earlier. We wished to see if a similar lethal reaction could be produced by the individual component proteins of cow's milk.

The guineapigs were sensitised as before by injecting intraperitoneally 2% w/v reconstituted National dried milk in a dose of 1 ml. On the 69th day they were challenged via the respiratory tract while under light anæsthesia with 0·25 ml. of: (*a*) the soluble proteins in 10% w/v reconstituted milk powder (approximately 1% soluble proteins), (*b*) 1% casein, (*c*) 1% α-lactalbumin, or (*d*) 1% β-lactoglobulin. The day before challenge each animal was bled and the serum subsequently tested for antibodies to reconstituted dried milk, and to the component protein with which the guineapig was challenged.

The results of the serological tests, and the clinical effects on challenge are recorded in table II. Casein, as might be expected, proved to be as effective as whole milk in producing lethal reactions. In one of the previous papers (Gunther et al. 1960) similarly sensitised guineapigs tested 17 days after injection had antibodies to α-lactalbumin but none to β-lactoglobulin. In the present experiment no antibodies could be shown to α-lactalbumin 69 days after injection. Clinically only very mild reactions were produced on challenging with α-lactalbumin, but with β-lactoglobulin the reactions were as severe as with casein or whole milk.

TABLE II—LEVEL OF SERUM ANTIBODY TO MILK PROTEINS ON 69TH DAY AFTER INJECTION AND CHALLENGE OF SENSITISED GUINEAPIGS WITH COMPONENT PROTEINS OF COW'S MILK

Guinea-pig	Challenged with	Serum antibody titre to				Clinical effect on challenge‡
		Reconst. National dried milk	Casein	α-lact-albumin	β-lacto-globulin	
1	Soluble material in reconstituted National dried milk*	16	..	..	..	++
2		16	..	..	..	D
3		32	..	..	..	+++
4		16	..	..	..	D
5		..	..	..	..	D
6	Casein†	8	16	..	..	D
7		16	16	..	..	++
8		128	64	..	..	D
9		16	16	..	..	D
10		16	16	..	..	D
11	α-lactalbumin†	8	..	0	..	+
12		32	..	0	..	+
13		32	..	0	..	+
14		8	..	0	..	W
15		16	..	0	..	−
16	β-lactoglobulin†	16	..	..	0	D
17		8	..	..	0	++
18		4	..	..	0	D
19		64	..	..	32	D
20		64	..	..	4	D

0 indicates a titre <2.
Scale of severity of clinical effects—see table I.
* Made up 10% w/v—approximately 1% soluble protein.
† A 1% solution.
‡ Of thirty unsensitised (control) anæsthetised guineapigs challenged with soluble or insoluble milk preparations (Parish et al. 1960) no reaction was observed in twenty-six—one showed a very mild reaction and two a moderate reaction. One animal died, but on subsequent investigation its serum was shown to contain what appeared to be a naturally occurring antibody to cow's milk proteins to a titre of 16.

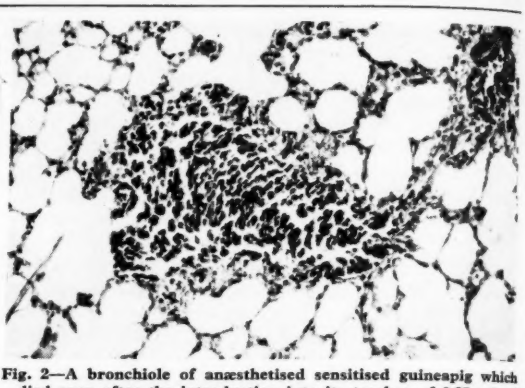

Fig. 2—A bronchiole of anæsthetised sensitised guineapig which died soon after the introduction into its trachea of 0·25 ml. of diluted (50%) stomach contents from a case of cot death. (Hæmatoxylin and eosin. ×120.)

The bronchiole is so full of desquamated epithelial cells that in the photograph it is scarcely recognisable.

We have thus shown that lethal reactions can be produced with casein and β-lactoglobulin. On the other hand only mild reactions were obtained with α-lactalbumin. However, further guineapigs will have to be tested at different periods after sensitisation before this protein can be considered less noxious than the other two.

Pathological Findings in Sensitised Guineapigs

The histopathology of the lungs of sensitised guineapigs which died after inhalation, when anæsthetised, of total reconstituted dried milk, or its soluble or insoluble fractions, has already been described (Parish et al. 1960). All the changes observed in the lungs of similarly sensitised guineapigs which died after the inhalation of casein or β-lactoglobulin closely resembled those in the earlier experiments. In those sensitised animals challenged with β-lactoglobulin or casein, the chief features were generalised congestion with occasional areas of partial collapse, and serous exudate or œdematous transudate. Cellular infiltration in the œdematous areas, or in the peribronchial, or periarteriolar connective tissue consisted chiefly of mononuclear cells. Many of these were macrophages with variable numbers of lymphocytes and, in some animals, plasma-cells; but there were few polymorphonuclear cells. A common finding was the desquamation of large numbers of single, intact, apparently normal, epithelial cells of the bronchial wall into the lumen of the small bronchioles.

The histopathological changes in the lungs of sensitised anæsthetised guineapigs which had died as a result of inhaling small amounts of the stomach contents obtained from cot-death cases were similar to those observed in sensitised animals inhaling milk. Generalised congestion was usual, but there was only an occasional small area of œdema and little cellular infiltration. The infiltrating cells were chiefly macrophages, though there was an increased number of polymorphonuclear leucocytes—more than observed in animals challenged by milk. The majority of the leucocytes were eosinophils, and in some preparations they were found also in the peribronchial connective tissue. There was some evidence that the bronchioles and arterioles had undergone contraction, but further study of this feature is required. Many of the medium-sized and smaller bronchioles contained large numbers of desquamated cells; sometimes these completely filled the lumen (fig. 2). Bronchioles thus affected could be found in all the lung material, but the number varied from animal to animal. The trachea was usually congested and in some cases infiltrated by eosinophils; the epithelium of the trachea was not desquamated.

The unsensitised—i.e., normal anæsthetised control guineapigs which had inhaled the stomach contents obtained from the same human subjects, and subsequently killed by an

overdose of pentobarbitone—had different histopathological changes in their lungs. There were large areas of partial collapse and œdema, or serous exudate, infiltrated with moderate numbers of macrophages and polymorphs of both the heterophil and eosinophil type. All areas of the lung were congested and there was an occasional small hæmorrhage into the alveoli. The epithelium of the majority of the bronchioles was intact; if it was not, the desquamation was in the form of sheets or strips of epithelium, and for the most part the individual cells were not detached from one another (fig. 3).

The differences in degree of œdema and cellular infiltration between the unsensitised and sensitised guineapigs challenged with human stomach contents probably depend on the time that the irritant material remained in the living animal. The majority of the sensitised animals died within 5 minutes, and all within 10 minutes, whereas the unsensitised animals were killed about 3 hours after challenge. Previous experiments on normal animals revealed that the mode of killing by pentobarbitone did not cause changes of this type.

The histopathological findings in sensitised guineapigs, dying after inhalation of milk proteins, are very similar to those described and illustrated in cot death by Barrett (1954) and Stewart (1957). The lungs of cot-death subjects are usually congested, and the engorgement of the capillaries is often accompanied by œdema, small hæmorrhages, foci of partial collapse, and an increase in the number of macrophages in the alveoli. The walls of the bronchi are infiltrated by lymphocytes and plasma cells; sometimes there are also smaller numbers of polymorphonuclear leucocytes. Desquamation of the bronchial epithelium is commonly seen (figs. 4 and 5) and is often of the type described by Bodian and Heslop (1956), who thought that the presence within the bronchi of large numbers of individual desquamated cells embedded in mucus was characteristic of cot death, although it did not occur in every case.

All of these histopathological features of cot death were also seen in the sensitised anæsthetised guineapigs which died after inhalation of small amounts of milk, or of stomach-contents containing milk. Perhaps the most significant common finding was the presence of large numbers of individual intact epithelial cells in the lumina of the bronchioles. The appearance was the same as that described by Bodian and Heslop (1956) except that in the guineapigs there was little if any mucus. This difference may be due to an anatomical difference between man and guineapig, for there are very few mucous glands in the trachea and bronchi of the guineapig, and few goblet-cells in the epithelium. Another difference between the human and the animal material is that in the guineapigs no desquamation of epithelium was observed in the trachea, though it occasionally occurred in the large bronchi. Desquamation of epithelium is, however, a common postmortem change, which would be expected to be greater in the human than in the animal material because of the unavoidably longer interval between death and necropsy.

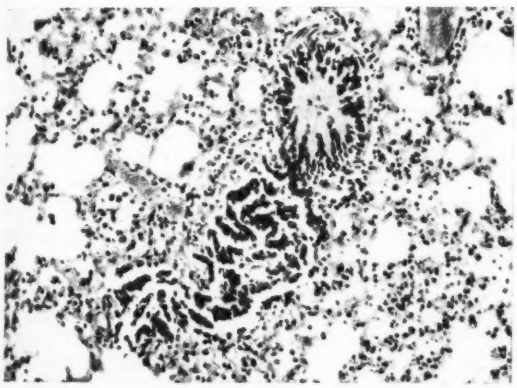

Fig. 3—Bronchioles of an unsensitised guineapig which was killed 3 hours after receiving the same dose of the same stomach contents as fig. 2. (H. & E. ×120.)

The introduction of the stomach contents was without clinical effect. The upper bronchiole is normal; the bronchiolar epithelium of guineapigs is normally more folded than that of man. In the lower bronchiole, the lumen is occupied by strips of detached epithelium, but the appearance is different from that in fig. 2.

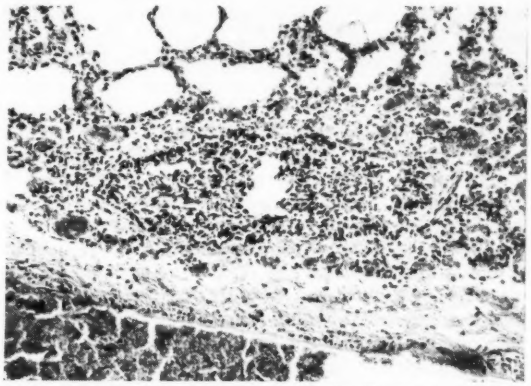

Fig. 4—Bronchiole from case of cot death, showing lumen filled with desquamated epithelial cells. (H. & E. ×100.)

Discussion

Sudden death of infants is by no means uncommon, and the Registrar General's data showed that in England and Wales in 1955, there were 1432 such deaths accounting for 20·5% of the 6993 deaths between the ages of 2 weeks and 2 years (Banks 1958).

The usual history is that of a baby dying in its sleep. As a rule the babies are between 1 month and 6 months of age, though the incidence appears to be highest at about 3 months. These deaths are attributed by many to a fulminating infection, although attempts to demonstrate a causal organism, either bacteria or virus, have been unsuccessful in most cases (Banks 1958).

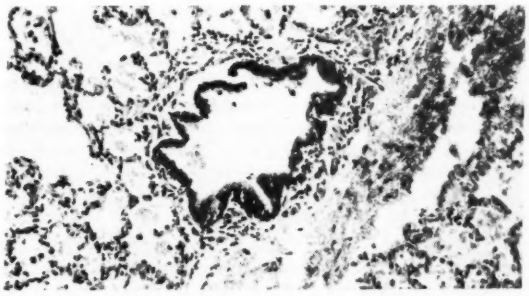

Fig. 5—Bronchiole of infant believed to have died of suffocation. (H. & E. ×100.)

The epithelium is intact except at the top left, where it has become partially detached. Such detachment often occurs post mortem.

x2

The most common foreign proteins to which a baby is exposed are those of cow's milk, either as fresh milk, or as a preserved-milk product, which is also a constituent of proprietary preparations for infants. It has previously been shown that babies may be sensitised to milk products (Anderson and Schloss 1923, Tallerman 1934) and this sensitivity may cause disease on contact with the milk antigen (Clein 1958). In the preliminary experiments, where examination was made of the sera of normal babies between 7 and 97 weeks of age for agglutinating antibodies to cow's milk, the large majority were found to have been "immunised" to some degree or other, and their tissues were probably sensitised by some form of antibody as a result of this immunisation (Gunther et al. 1960). When, as in fig. 1, the antibody titres to milk in the serum of babies believed to be typical cases of cot death are superimposed on those obtained from normal infants, it can be seen that in any age group the titres of the cot-death cases tend to be high when compared with the normal, indicating that a considerable degree of sensitivity could be present.

In experiments performed on guineapigs (Parish et al. 1960), which have been confirmed by the data presented in this paper, it was found that sensitised guineapigs in an anæsthetised state died after inhalation of milk proteins. Death was not typical anaphylactic shock as observed in the conscious state, but the animal, without any struggle, stopped breathing either at once or after a brief episode of irregular respiration. Animals not sensitised to milk could inhale up to 1·0 ml. without significant effect. The histopathological changes following challenge of the sensitised animals had much in common with those described in cases of cot death in infants.

It has thus been demonstrated that sensitised animals, when unconscious, can be killed quickly, silently, and without trace of struggle by the inhalation of whole milk, or, at least, by two constituent proteins of milk, casein and β-lactoglobulin.

It is well known that babies frequently regurgitate small quantities of food during sleep and often leave traces on the pillow. In our hypothesis it is suggested that inhalation of regurgitated material can induce a lethal reaction, and that only small amounts need be aspirated. The quantity aspirated by the infant may be of the order of 1·0 ml., on a comparison of the weights of the test guineapigs and cot-death subjects.

We have been able to show that many babies have some antibody to cow's milk, and that guineapigs with a similar serum-antibody level can be killed quietly by aspiration of small quantities of milk.

If the challenge agent in babies were food material from the stomach regurgitated during sleep, it had to be shown that this material retained its antigenic properties sufficiently to cause shock on contact with tissues sensitised to milk. This was found to be so. The stomach contents taken from 4 cases of cot death in which the infants were known to be bottle-fed, when inhaled in small amounts by lightly anæsthetised guineapigs sensitised to milk proteins, resulted in death, quietly and without struggle, in 15 of the 19 challenged animals. The histopathological features were similar to those observed in cot death of infants. An equal number of anæsthetised guineapigs, not sensitised to milk proteins, which had inhaled the same stomach-content material displayed no effects, or scarcely appreciable respiratory embarrassment, and there were no deaths.

These experiments provide a model of a possible cause of cot death in infants. If the serum level of antibody is a valid indication, the majority of babies are sensitised to some degree to cow's milk, and it is possible that a normal healthy baby may be put to bed, and, during its sleep regurgitate and inhale sufficient material to cause an antigen-antibody reaction in the sensitised tissue of the lungs, causing physiological and pathological changes resulting in the death of the infant.

Further investigation of this problem is being undertaken. An attempt is being made to prove that an antigen-antibody reaction has taken place in the lungs of such infants and that this reaction is of sufficient magnitude to cause death. The nature or the degree of the sensitivity may be an important factor, for the number of babies that have a substantial titre of circulating antibodies to milk is large compared to the small number of cot-death cases, though another limiting factor may be the frequency with which aspiration occurs. Nevertheless, the fact that babies do become sensitised to cow's milk proteins, and that inhalation of this material could conceivably be the cause of cot death in a young infant, should be another inducement to breast-feed young babies where practicable.

Summary

Experimental evidence is presented to support the hypothesis that cot death in infants may be due to an anaphylactic type of reaction consequent on the inhalation of cow's milk proteins regurgitated from the stomach during sleep.

Serological tests show that most infants fed on cow's milk develop antibodies to milk proteins.

Experiments on anæsthetised guineapigs, sensitised to the proteins of cow's milk, show that many such animals die rapidly and without struggling when a small quantity (0·25 ml.) of: (*a*) cow's milk, (*b*) stomach contents from cases of "cot death", (*c*) a 1% solution of casein, or (*d*) a 1% solution of β-lactoglobulin is introduced into the air passages.

The histopathological changes in the lungs of the experimental animals resemble those found in cases of cot death.

We wish to acknowledge the helpful discussion with the members of the steering committee and the scientific subcommittee of the "Enquiry into sudden death in infancy" under the respective chairmanships of Prof. Leslie Banks and Sir Samuel Bedson and to thank this body and the Nuffield Foundation for a grant to cover the cost of animals used in these experiments. They are most grateful to Dr. H. R. M. Johnson for his help in the collection of material from cot-death cases, and to Dr. N. R. Butler and the pædiatric staff, University College Hospital, for their help in obtaining serum-samples.

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EFFECT OF PHENINDIONE AND BED REST ON BLOOD COAGULABILITY FOLLOWING A HIGH-FAT INTAKE

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RECENTLY we have shown that, when careful attention is paid to technique, the recalcified-plasma-clotting (R.P.C.) time is an accurate measure of in-vitro coagulability (McDonald and Fullerton 1958a). With further experience of this technique, in more than 200 samples of plasma, duplicate readings have given a mean difference of less than 3 seconds and a maximum difference of 7 seconds. A smooth non-traumatic venepuncture is essential. When this is achieved the mean difference between samples obtained from both arms in 15 patients was only 3·5 seconds, and in only 1 case was this difference

TABLE I—SIMULTANEOUS R.P.C. TIMES (SEC.) IN BOTH ARMS: VENEPUNCTURE UNSATISFACTORY IN ONE ARM

Subject no.	Satisfactory arm	Unsatisfactory arm	Difference
1	103	75	28
2	124	110	14
3	130	115	15
4	87	73	14
5	127	93	34
6	147	96	51
7	117	91	26
8	137	110	27
9	124	59	65
10	123	103	20
11	95	47	48
12	130	113	17
13	131	116	15
14	115	93	22
Means	120·7	92·4	28·3

greater than 8 seconds, which we take as the upper limit of experimental error (McDonald and Fullerton 1958a). Difficulty in venepuncture shortens the R.P.C. time. This is clearly shown in table I, which gives simultaneous R.P.C. times for both arms in 14 patients. The venepuncture was satisfactory in one arm; in the other it was unsatisfactory in that tissue trauma was produced, either inadvertently or by design. It is seen that the readings in the samples obtained by unsatisfactory venepuncture were consistently much shorter, the mean difference being 28·3 seconds.

By this technique we have shown that (1) a high-fat breakfast containing 85 g. animal-fat (bacon, eggs, butter, tea with milk and sugar) resulted in a pronounced shortening of the R.P.C. times measured 3 and 4 hours after the meal (McDonald and Fullerton 1958a); (2) a similar reduction occurred after approximately the same amount of vegetable fat (McDonald and Fullerton 1958a); and (3) the effect of the high animal-fat breakfast was almost completely abolished by a moderate amount of physical activity (McDonald and Fullerton 1958b).

TABLE II—GROUP 1: RECENT CARDIAC INFARCTION; PHENINDIONE; BED REST

Subject no.	Fasting	3½ hr.	Difference
1	126·5	117·5	+9
2	163	162	+1
3	151	143	+8
4	146·5	133·5	+13
5	134	131	+3
6	133	136·5	−3·5
7	142	131	+11
8	177	176	+1
9	138	146	−8
10	160	159	+1
Means	147·1	143·5	+3·6

The object of the experiments reported here was primarily to assess the effect of therapeutic doses of phenindione on this increase in coagulability following a high fat intake.

TABLE III—GROUP 2: NON-CARDIAC DISORDERS; NO PHENINDIONE; BED REST

Subject no.	Fasting	3½ hr.	Difference
1	104·5	74·5	+30
2	122	74	+48
3	102·5	69·5	+33
4	125·5	59·5	+66
5	111	76	+35
6	111·5	90	+21·5
7	102	72·5	+29·5
8	114	102	+12
9	116	100·5	+15·5
10	107	86	+21
Means	111·6	80·4	+31·2

Clinical Material and Methods

The methods used in these experiments and the details of the animal-fat breakfast (fat content, approximately 85 g.) have been described previously (McDonald and Fullerton 1958a). Four groups have been studied in this way:

Group 1: 10 inpatients at rest in bed, with recent cardiac infarction, treated with phenindione for periods varying from 4 to 18 days.

Group 2: 10 inpatients at rest in bed, with non-cardiac disorders, and not treated with phenindione.

Group 3: 10 outpatients with previous cardiac infarction who had had long-continued therapeutic doses of phenindione for periods varying between 12 and 45 months.

Group 4: 10 outpatients who had had a cardiac infarction and had received 1 mg. phenindione daily for periods ranging between 20 and 41 months. This group was drawn from the controls in the Medical Research Council (1959) trial of long-term anticoagulant administration after cardiac infarction.

The subjects in groups 3 and 4 were allowed to undertake some physical activity, in contrast to the subjects in groups 1 and 2 who were confined to bed both during and for several days before the experiment. They reached hospital by walking varying distances and by using public transport, and, after the high-fat breakfast had been taken, they were allowed to walk short distances from time to time in the ward corridors.

TABLE IV—GROUP 3: OLD CARDIAC INFARCTION; PHENINDIONE; AMBULANT

Subject no.	Fasting	3½ hr.	Difference
1	148	146	+2
2	123	125·5	−2·5
3	144	149·5	−5·5
4	187	174	+13
5	140	134	+6
6	188·5	176	+12·5
7	144·5	139	+5·5
8	127	134	−7
9	141	141·5	−0·5
10	130	131	−1
Means	147·3	145	+2·3

In groups 1 and 3 the one-stage "prothrombin-time" was maintained at 2 to 2½ times the control level, whereas in group 4 it was within the normal range. No patient in group 2 had a disorder likely to be associated with an abnormality of blood coagulation.

In addition to estimations of the R.P.C. times, the degree of lipæmia in each sample of plasma was measured by assessing the turbidity by a modification of the method described by Schwartz et al. (1952). Direct measurement of light transmittance was obtained with a Spekker photoelectric absorptio-

TABLE V—GROUP 4: OLD CARDIAC INFARCTION; 1 MG. PHENINDIONE; AMBULANT

Subject no.	Fasting	3½ hr.	Difference
1	116	116	0
2	102	92	+10
3	152	130	+22
4	124	97	+27
5	138	117	+21
6	145	125	+20
7	139	118	+21
8	130	110·5	+19·5
9	116·5	96	+20·5
10	105	98·5	+6·5
Means	126·7	110	+16·7

TABLE VI—MEAN PERCENTAGE INCREASE IN TURBIDITY AND REDUCTION OF R.P.C. TIME (SEC.) IN THE FOUR GROUPS

Group no.	Increase in turbidity	Reduction in R.P.C. time
1	205	3·6
2	337	31·2
3	80	2·3
4	123	16·7

meter and expressed as the direct scale reading. Glass cuvettes with a 2 mm. light path and a blue filter (Ilford Spectrum Blue, 602) with maximum transmittance at 4700 Å were used.

Results

The results are presented in tables II–V, which show the R.P.C. times of all the subjects fasting and during the phase of lipæmia 3½ hours after the meal. It is seen that in subjects in groups 1 and 3 who were receiving therapeutic doses of phenindione, the fasting R.P.C. times were slightly prolonged but the high-fat meal had no consistent effect on the R.P.C. times during the lipæmic phase 3½ hours after the meal. In group 1 the greatest reduction was only 13 seconds and the mean reduction 3·6 seconds. In group 3 the corresponding figures are 13 seconds and 2·3 seconds. In group 4, receiving only 1 mg. phenindione daily, the results were strikingly different. In 8 of the 10 subjects the R.P.C. times 3½ hours after the high-fat meal were considerably shorter than the readings during fasting, and the mean reduction was 16·7 seconds. This result is similar to that found in a group of 16 students who undertook little physical activity after the high-fat breakfast (mean reduction 23·8 seconds) (McDonald and Fullerton 1958b). In group 2 the mean reduction in R.P.C. time 3½ hours after the meal was still greater—31·2 seconds. This is similar to the results found previously in 11 subjects confined to bed; in them the mean reduction in R.P.C. time 3 hours after the high-fat breakfast was 39 seconds, and at 4 hours 35 seconds (McDonald and Fullerton 1958a).

Discussion

The results demonstrate that the ingestion of a high-fat breakfast by patients receiving therapeutic doses of phenindione (groups 1 and 3) does not produce the acceleration of the R.P.C. time found in subjects not receiving this drug (groups 2 and 4). So far as we know this action of phenindione has not been demonstrated previously; its mechanism is obscure. Clearly, however, it does not depend entirely upon an alteration in the degree of plasma turbidity during the lipæmic phase. Table VI shows the mean percentage increase in turbidity 3½ hours after the high-fat meal, and the mean decrease in the R.P.C. time in the four groups of subjects. In both groups of ambulant patients (groups 3 and 4) the increase in turbidity was less than in the patients at rest in bed (groups 1 and 2). But in group 1 the increase in turbidity was greater than in group 4, whereas the mean reduction in R.P.C. time in group 1 was negligible and in group 4 it was considerable.

A comparison of the findings in groups 2 and 4 has confirmed our previous impression that the reduction in R.P.C. time is considerably greater in subjects confined to bed in hospital. It seems that even the small amount of physical activity undertaken before and after the ingestion of the high-fat breakfast by the subjects observed as outpatients (group 4) offsets to some extent the increase in coagulability during the phase of lipæmia. Further studies along these lines are at present in progress.

The practical importance of the effect of phenindione which we have demonstrated is at present conjectural. Because of the differences between the process of clotting in vitro and intravascular thrombosis, it is perhaps unwise to draw firm conclusions from results obtained with the R.P.C. test and other laboratory tests of blood coagulability. Nevertheless one essential feature common to clotting in vitro and intravascular thrombosis is fibrin formation, and it is not unreasonable to suggest that factors which can be shown to accelerate this process in vitro may also operate when intravascular thrombosis occurs.

Many physicians treat patients with cardiac infarction with phenindione and by restricting their fat intake. If shortening of the R.P.C. time following a high-fat meal reflects increased coagulability in vivo and, therefore, an increased tendency to thrombus formation, there may be nothing to be gained by lowering the fat intake of patients receiving phenindione. Moreover, it seems possible that the beneficial effect of phenindione in cardiac infarction may be due partly to its action in abolishing the increase in coagulability after high-fat meals.

Summary

Shortening of the recalcified-plasma-clotting (R.P.C.) time following the ingestion of a high-fat meal was *not* found in patients receiving therapeutic doses of phenindione.

In subjects not receiving phenindione the shortening was greater in patients confined to bed than in those who were ambulant.

We are grateful to Sister I. M. Cowie, ward 1, Aberdeen Royal Infirmary, for much help, and to the patients for their cooperation.

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MEDICAL TREATMENT OF MYCETOMA

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MYCETOMA is the name applied by H. V. Carter to a fungal infection prevalent in Southern India, which was locally termed Madura foot. Although still often used for this low-grade fungal parasitism, the latter term is undesirable because it suggests an exclusive geographical and anatomical localisation.

Mycetoma occurs predominantly in underdeveloped areas which have rudimentary medical facilities and often no auxiliary medical departments. Thus we can hardly

expect full mycological identification of the responsible organism in each case. Ideally specific chemotherapy depends upon identification and culture of the organism, determination of its sensitivity to a range of drugs, and exhibition of the appropriate drug. But even with the best of facilities culture is difficult and identification is a matter of experience and special training, whilst details of suitable drugs are at present mainly to be found in specialised journals, reports of their efficacy sometimes being difficult to evaluate. Consequently an outlook of therapeutic nihilism has prevailed as far as mycetoma is concerned, and the treatment has almost invariably been surgical ablation of the affected tissues.

Although not a killing disease, mycetoma causes a fair amount of morbidity and disablement—disablement which is little alleviated by amputation unless prostheses are available. The effect upon a wage-earner and his family—the disease is primarily of active males—can well be disastrous.

Fig. 1—Left hand (*a*) on admission, and (*b*) 6 months later.

In these particular social and medical circumstances any drug advocated must have a wide range of effectiveness against the many possible causative organisms, and it must also be safe, cheap, and easy to administer. A simple scheme of treatment, giving a satisfactory overall "cure" rate, is more likely to gain widespread acceptance than a more definitive but complex scheme, although a few cases may not respond to this shot-gun method. Whatever the method there are still some fungi for which no specific therapy is yet known. For those patients who fail to respond to chemotherapy amputation is still available.

In Ibadan we have treated cases of mycetoma with a preliminary course of a wide-spectrum antibiotic, to eradicate the almost invariable secondary infection, combined with a long course of dapsone (diaminodiphenylsulphone), and, when feasible, with immobilisation of the affected part. These patients were only admitted to hospital for a week or so until secondary infection had cleared, and they then continued to take dapsone, in a dosage of 100 mg. b.d., as outpatients. After initial observation for a month they need only attend hospital every 3 months, and this regime may be continued for anything up to 2 years.

Although surgery still plays a role in the treatment of mycetoma, it should not be invoked, except in special circumstances, until a reasonable course of medical treatment has been tried. Orthopædic surgeons expect that bone and joint tubercle and leprosy require long-continued exhibition of drugs, and the same attitude should eventually prevail in the treatment of mycetoma. Early surgery is probably justifiable in strictly localised forms of the disease, particularly the nodular superficial varieties caused by the black-grain *Madurella mycetomi*.

Eight of a group of eighteen cases which we treated in Ibadan without radical surgery have responded, showing closure of sinuses, and clinical and radiographic improvement, and they have returned to their previous work. We have been unable to follow all the patients because some defaulted or continued their course elsewhere—these have been assumed to be failures. To know whether the "clinical cure" persists will require a longer follow-up, but at least these patients still have the use of their limbs.

The dramatic response which can follow this treatment is shown by the following case-histories:

Case 1.—A 40-year-old Yoruba farmer came to hospital complaining of progressive swelling of the left hand, and of multiple discharging sinuses, which had been present for 3 years. These had prevented him from working for the past year. He was ashamed of his enormous foul-smelling hand, and kept it covered up and hidden within his gown.

Multiple sinuses and ulcerated areas were present over both surfaces of the hand, and much foul discharge was exuding. No grains could be seen. The axillary lymph-glands on the same side were large and tender. A radiograph of the hand disclosed extensive periosteal new bone enveloping the metacarpals and phalanges, and this was considered typical of a nocardial type of mycetoma, with secondary infection. No fungal elements were observed in the pus, and only *Escherichia coli* was isolated on culture. Biopsy of skin and subcutaneous tissues revealed a chronic inflammatory reaction, but no grains could be demonstrated. Despite these negative bacteriological findings a definite clinical diagnosis of mycetoma was made.

Tetracycline, 250 mg. q.i.d. was given for a week, and in addition dapsone 100 mg. b.d. was started. The patient continued on the drug for 2 years. A month after starting treatment the hand had returned to more normal proportions and all the sinuses had healed. Within 6 months of his first attendance the patient was again at work in the fields. His hand is now completely healed, but the range of movement is limited partly by scarring but more so by degree of subluxation of his wrist which causes passive insufficiency of his flexors. Now that the lesion is quiescent orthopædic procedures are envisaged to give a more useful hand (fig. 1).

Case 2.—A Yoruba tailor, aged 45, attended hospital because of progressive swelling of his left hand for 7 months and ulceration of his left axilla for the previous 3 months. Because of this disability he had been unable to work. The left hand was greatly swollen with multiple puckered sinuses exuding a thin serous discharge. There were areas of ulceration in the axilla and on the chest wall (fig. 2). A radiograph of the hand showed typical changes of nocardial-type diffuse mycetoma. A biopsy specimen was taken but the tissue only revealed a chronic inflammatory reaction, and no grains. A nocardia species was obtained from culture of the pus, but full identification was not possible as the strain died out. *Esch. coli* also grew from the pus.

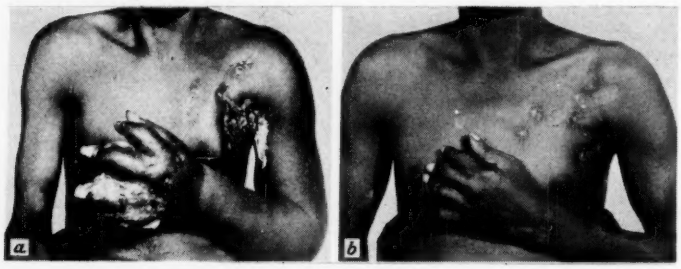

Fig. 2—Appearance of case 2 (*a*) on admission, and (*b*) 7 months later.

This clinical type of mycetoma, with early invasion of the thorax, is very serious and occasionally fatal, and justifies energetic treatment. Penicillin 2 million units was given daily for 3 months, and at the same time dapsone 100 mg. was given twice a day by mouth. The ulceration in the axilla slowly healed during the first 3 months, and the sinuses of the hand had closed at the end of 6 months. The patient now has an efficient hand and is again working as a tailor. The course of dapsone lasted 2 years, during which time he showed no evidence of toxic reactions.

Case 3.—A 20-year-old farmer came to the surgical outpatient department with a swollen discharging left foot. Sinuses were present on the greatly swollen dorsum of the foot, and the inguinal glands on that side were enlarged and hard. A radiograph revealed a destructive lesion of the second metatarsal, and some periosteal reaction near the head of this bone, which was reported as being probably due to mycetoma. As no fungal elements could be recovered from the discharge, the lesion was considered tuberculous by the clinician and accordingly treated with *p*-aminosalicylic acid and isoniazid for 3 months without improvement.

The patient was then admitted to hospital, and the foot was explored, with removal of the metatarsal and curetting of the sinuses. The bone showed on section grains morphologically identical with *Nocardia braziliensis*. The patient was given dapsone 100 mg. b.d. for a period of 18 months. 4 months after the operation the foot had completely healed and the patient had returned to work. Surgery was probably not necessary in this case, but this form of local resection, with chemotherapeutic cover, may have led to more rapid healing.

Discussion

Mycetoma is caused by a wide variety of organisms of different genera and species, and it presents by its very nature several features which tend to render it resistant to chemotherapy.

Firstly, although the pathological processes may vary in degree of severity from the localised *M. mycetomi* infections to the infiltrating lesions of *Allescheria boydii* and *Streptomyces pelletieri*, yet, in virtually all cases, the fungal elements occur within relatively avascular tissue resulting from scarring and local endarteritic changes.

Secondly, once sinuses have developed pyogenic secondary organisms invade the lesion.

Thirdly, the disease is caused by a variety of species each differing from the rest in its drug sensitivity, and even isolates of the same species may vary in their response from case to case.

Because of the wide variety of causative organisms a single drug is unlikely to prove effective against all the possible organisms of mycetoma. A further factor to be borne in mind is the geographical distribution of the different organisms. A complete survey of this is impossible here; but, for example, in Southern Arabia and the Sudan the common organisms are *M. mycetomi*, *Strep. somaliensis* and *Strep. pelletieri*, whereas in Western Nigeria *N. brasiliensis*, *M. mycetomi* and *All. boydii* are probably the most frequent.

The best therapeutic regime will probably vary according to the main species in any particular locality. We do not suggest that our scheme of treatment is the only one, or even the best, but we have found it effective in salvaging limbs, and it is cheap. Though blind therapy in a sense, it is suited to the conditions of practice where mycetoma is most frequent. The basic principle of a course of antibiotics and prolonged drug administration, combined with immobilisation by sling or plaster-of-paris, seems to us rational. Much that was written on the chemotherapy of this disease before 1950 is now merely of historical interest. Some of the more recent developments have been reviewed by one of us (Cockshott 1957) and this paper can be consulted for more detailed references.

Dapsone, though first synthesised in 1907, found no pharmacological application until 1937, when it was discovered to be effective in treating experimental streptococcal infections but it was too toxic for man in the dosage then being employed. Dapsone possesses a degree of antituberculous activity, but its main use has been in the treatment of leprosy caused by acid-fast mycobacteria. Ochoa found that dapsone was effective in vitro against the acid-fast nocardia, which causes some varieties of mycetoma, and systemic nocardiosis. Encouraged by these tests he started treating mycetoma due to *N. brasiliensis* with this drug, and the results were excellent (Ochoa 1955, Ochoa and Macatola 1955). Various other workers (Halde and Newstrand 1955, Mackinnon et al. 1958) have shown that dapsone is effective in causing inhibition of growth of *M. grisea*, *Strep. maduræ*, and *Strep. somaliensis*, as well as *N. brasiliensis*. The antifungal activity of this drug probably depends upon substrate competition for paraminobenzoic acid (Cockshott 1957).

Although the dosage of dapsone we have used may seem high, it appears to be safe. We advise close observation during the first month to enable early detection of exfoliative dermatitis or hæmolytic anæmia in the occasional case. One of our patients developed exfoliative dermatitis, and his therapy had to be discontinued.

Summary

A plea is made for a more optimistic outlook in the treatment of mycetoma. A regime based on a short course of wide-spectrum antibiotic and prolonged treatment with dapsone by mouth has been found effective. In nearly half our cases, this treatment has avoided the need for amputation and enabled the patient to get back to work.

We extend our thanks to the physicians and surgeons of University College Hospital, Ibadan, who have referred cases to us, and to Mr. Frank Speed, of the medical illustration department, for the photographs.

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EVALUATION OF THROMBOTEST IN THE CONTROL OF ANTICOAGULANT THERAPY

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CONTROL of anticoagulant therapy with coumarin or indanedione drugs has been based for many years on the one-stage prothrombin-time test of Quick (1935). Oral anticoagulant drugs undoubtedly lower the production of prothrombin, but the term "prothrombin-time" is somewhat of a misnomer, since it is factor VII which is mainly measured. Fortunately Quick's test is very sensitive to changes in factor VII activity. Drug dosage is so adjusted that prothrombin-times of $1^1/_2$–$2^1/_2$ times normal are obtained within a few days and maintained in this so-called therapeutic range. Quick (1938) demonstrated the hyperbolic relationship between prothrombin-times and prothrombin activity, normal prothrombin activity being 100%. Thus the "therapeutic range" is about 15–30% of normal if a saline extract of acetone-dried rabbit or human brain is used as thromboplastin reagent in the test.

During oral anticoagulant treatment hæmorrhages or further thromboses have sometimes been reported even where the greatest care has been taken to keep within the therapeutic range. In recent years it has been shown that, during treatment, factors involved in "intrinsic" blood-thromboplastin production—e.g., Christmas factor (factor IX), Prower-Stuart factor (factor X), and possibly others—are reduced. Quick's test does not register changes in Christmas factor because of the powerful tissue thromboplastin used.

Some workers are of the opinion that heparin-clotting-time methods give a better indication of impending complications (Soulier and le Bolloch 1951, Poller 1954) but, for technical reasons, such tests are not suited to the daily routine control of large numbers of patients on anticoagulants.

Owren (1959), in his 'Thrombotest' method, has modified the one-stage technique in order to produce a method capable of measuring "intrinsic" blood-thromboplastin factors as well as prothrombin and factor VII. The thrombotest reagent contains a thromboplastin of relatively weak activity, and it is claimed to possess some sensitivity to changes in Christmas-factor levels.

We made our present investigations to assess the value of the thrombotest method for the control of patients on phenindione ('Dindevan') therapy as compared with Quick's test and the prothrombin and proconvertin (P & P) test of Owren and Aas (1951). In view of the claims that thrombotest was sensitive to changes in blood-thromboplastin factors, it seemed essential to include a thromboplastin-generation test (T.G.T.).

Methods of Study

Forty-three inpatients undergoing phenindione anticoagulant therapy were studied. They were divided into two groups, A and B:

In group A, comprising thirty-one patients, dosage of the anticoagulant was based on the Quick prothrombin-time method, and observations were made of the effect on the P & P method, the T.G.T., and thrombotest. The clinical conditions included in this group were:

Coronary thrombosis	13
Pulmonary embolism	2
Venous thrombosis	2
Cerebral vascular disorders	3
Angina pectoris	8
Peripheral artery occlusion	3

In group B, which consisted of twelve patients, dosage was based on the result of thrombotest, and the observation was confined to the effect on the Quick prothrombin-time method and T.G.T. The cases included in this group were:

Coronary thrombosis	10
Pulmonary embolism	1
Prophylactic therapy	1

In group A, 415 blood specimens were tested during 530 days of treatment. In group B, 154 blood specimens were examined over 246 days' treatment.

Technique

Quick One-stage Prothrombin-time

Venous blood (5 ml.) was collected into a siliconed syringe (although siliconing of the syringe is not essential), and transferred to a bijou bottle containing a dried oxalate mixture (0·21 ml. of an aqueous solution containing 2·4% ammonium oxalate and 1·6% potassium oxalate dried at 37°C in an incubator for 36 hours). The blood and oxalates were thoroughly mixed. The blood was then centrifuged at 3500 r.p.m. in a 13×100 mm. test-tube for 5 minutes. The supernatant plasma was decanted into another tube. The thromboplastin reagent was prepared from acetone-dried human brain. A phenol-saline extract was prepared (Powell 1957) which gave normal prothrombin-times of 11–12 seconds. A dilution curve was obtained by the saline dilution of normal plasma; the results from six normal subjects were averaged. On this curve, readings of 19–30 seconds represented 30–15% prothrombin activity. The same batch of brain was used throughout the investigation. The calcium-chloride reagent used was 0·18% $CaCl_2$, and it was prepared from a stock 1% solution checked by chemical analysis. This reagent was warmed to 37°C before use.

The test proper consisted in pipetting 0·1 ml. thromboplastin reagent into a 10×70 mm. test-tube in a 37°C water bath, and allowing the reagent to warm up for at least five minutes. The reagent could be incubated up to 2 hours without deterioration. The test plasma (0·1 ml.) was then added, and the contents of the tube were mixed gently. Within 20 seconds of mixing, 0·1 ml. of the warm calcium chloride was added, a stopwatch being started simultaneously. The tube was tilted to and fro until a clot was seen to form. Three tests were made on each specimen, and the results averaged. All tests were performed within an hour of collecting the venous-blood specimen.

P & P Method of Owren and Aas (1951)

Venous blood (1·8 ml.) was collected into a siliconed syringe (although siliconing of the syringe is not essential), and transferred to a *siliconed* bijou bottle containing 0·2 ml. trisodium citrate (3·13%). The anticoagulant used in this test usually contains heparin to prevent activation of clotting factors by contact with glass. We preferred to use a siliconed container so that the same specimen of blood might also be used for the thrombotest, thus obviating the use of heparin which would interfere with the latter test.

The blood and citrate were thoroughly mixed, and the specimen was centrifuged in the same siliconed bijou bottle. Supernatant plasma (0·1 ml.) was removed immediately before the test, and the 1 in 10 dilution was prepared in the usual manner. The bovine plasma obtained from an abattoir was adsorbed twice with barium sulphate, as recommended by Biggs and Macfarlane (1957). The saline extract of human brain was obtained in the following way. Human brain was freed from meninges and blood-vessels, washed with distilled water, cut into small pieces, and transferred to a large mortar. Warm saline at 42°C was added in small quantities, and the

tissue was pounded with a pestle. In all 1500 ml. of saline was added. The thick supernatant suspension was distributed into 1 oz. screw-capped universal containers, incubated at 37°C for 30 minutes, and then centrifuged to give a clear supernatant which was distributed into bijou bottles. The bijou bottles were stored at −20°C. This extract was found to give clotting times of 30–32 seconds with normal plasma. A citrate-saline dilution curve was prepared in the usual way. The same batch of thromboplastin reagent was used throughout the investigation.

The same specimen of blood was used for both P & P test and thrombotest. The thrombotest was always performed before the P & P test; removal of plasma for the P & P test could otherwise have interfered with the thrombotest by altering the red-cell volume.

Thrombotest

Owren (1959) recommended that either venous or capillary blood could be used for this test. We decided to use venous blood only, because with capillary blood there is always the danger of contamination of the specimen with a high concentration of tissue thromboplastin. Non-wettable syringes and containers must be used for the collection of the venous-blood specimen, because contact with glass shortens the clotting times and gives misleading results for the assessment of anticoagulant dosage.

Apparatus

Waterbath at 37°C, containing a metal test-tube rack with holes to accommodate 10×70 mm. test-tubes.

Pipette for measuring calcium chloride (11 ml.) for reconstituting the lyophilised thrombotest reagent.*

Pipette (0·5 ml.) for thrombotest reagent.*

Pipette (0·1 ml.) for blood sample.*

Syringes and bijou bottles siliconed with dimethyl dichlorosilane reagent in a fume cupboard. The silicone reagent bottle was handled with protective rubber gloves. The fumes are dangerous if inhaled. The reagent was drawn into the syringes, left in contact for 1 minute, and returned to the stock bottle in the fume cupboard. The bijou bottles were filled to the neck, and after 5 minutes the reagent was carefully decanted back into the stock bottle. The barrels and plungers were separated and washed in slowly running tap water continuously for 10 days. The bijou bottles were treated similarly. A final rinse with distilled water was given, and the washings were found to be neutral with B.D.H. universal indicator. One coating with the silicone reagent seemed to provide a permanent non-wettable surface. For convenience a 2 ml. graduation mark was made on the exterior surface of the bijou bottles.

Chemically clean 10×70 mm. test-tubes.

Reagents

Thrombotest reagent.—The lyophilised reagent in an ampoule was reconstituted with the calcium-chloride solution (see below) by gently mixing and incubating the resulting suspension, at 37°C, in a water bath for 1 hour. The reagent was gently mixed before use. When not required the reagent ampoule was stoppered and stored at 4°C; it was found to be stable for 4 days if the precaution of storing at 4°C was carefully observed. Four batches supplied by the manufacturers were used, and these gave different readings with normal venous blood. Each batch was supplied with its own dilution curve. Normal readings varied from 34 to 43 seconds with different batches of reagent.

Calcium chloride (3·2 mM solution).

Venous blood was collected as for the P & P test with a siliconed syringe. Thus the same specimen could be used for the two tests. Venous blood (1·8 ml.) was added to the 0·2 ml. trisodium citrate (3·13%) anticoagulant in the graduated bijou bottle. The contents were gently mixed. In all other respects the technique was as described by Owren (1959).

Procedure

Thrombotest reagent (0·5 ml.) was pipetted into a 10×70 mm. test-tube and left to warm in the 37°C bath for at least 3 and not more than 30 minutes. The venous-blood sample was gently mixed, and as 0·1 ml. was pipetted into the tube containing the thrombotest reagent a stopwatch was started simultaneously The tube was gently tilted in the waterbath. until a firm solid clot had formed. The percentage activity was then read from the dilution curve supplied by the manufacturers of the reagent.

Thromboplastin-generation Test

The procedure was as described by Biggs and Douglas (1953), except for the use of brain extract instead of platelet suspension (Bell and Alton 1954). The 6-minute reading was used for assessing the rate of thromboplastin generation. The results were related to a dilution curve prepared each day from a normal subject. The results of the T.G.T. were plotted graphically for each patient during the course of treatment, and compared with the graphed results of the Quick, P & P, and thrombotest methods.

The correlations between T.G.T. and each of the three methods mentioned above were then broadly assessed as being good, moderate, or poor in the forty-three patients investigated.

To check the constancy of the results of the T.G.T. a control group, comprising six hospital patients with no clinical evidence of thrombosis, was studied daily for 10 days. The test was found to give consistent results with the same batch of platelet substitute.

Results

Detailed results are shown in table I.

Group A

The patients in this group were controlled by the Quick test and were kept within the accepted therapeutic range (15–30% prothrombin activity) for over 80% of the period of treatment.

All patients were tested before treatment and then daily until the therapeutic range was reached. All results were included in the analysis, but had the initial results been excluded the proportion of tests within the therapeutic range would have been even higher.

The P & P test and thrombotest correlated well throughout, but the results were not directly comparable with those of the Quick test. Patients were within the P & P therapeutic range (10–30% activity) for only about half the period of treatment. For the thrombotest, it has been suggested by Owren that the therapeutic range is also 10–30% activity. Patients were only maintained within this thrombotest range for about two-thirds of the period of treatment.

Many results were below the lower limit of the thrombotest and P & P therapeutic range—i.e., less than 10% activity. On the other hand, with the Quick test very few were below its lower limit—i.e., less than 15% prothrombin activity.

Group B

The patients in this group were controlled by thrombotest, and these results were compared with the results of the Quick test.

* Pipettes specifically designed for the test can be obtained commercially if necessary.

TABLE I—COMPARISON OF THE RESULTS (IN TEST DAYS) OF QUICK, P & P, AND THROMBOTEST METHODS

Group	No. of patients	Total no. of test days	Total days' treatment	Quick (range 15 to 30%)		P & P (range 10 to 30%)		Thrombotest (range 10 to 30%)	
				Results above range	Results below range	Results above range	Results below range	Results above range	Results below range
A	31	415	530	76 (*18·3%*)	6 (*1·5%*)	16 (*3·9%*)	178 (*42·9%*)	12 (*2·9%*)	127 (*30·6%*)
				within range *80·2%*		within range *53·2%*		within range *66·5%*	
B	12	154	246	45 (*29·2%*)	1 (*0·7%*)			8 (*5·2%*)	29 (*18·8%*)
				within range *70·1%*				within range *76·0%*	

Over three-quarters of the patients were kept within the recommended 10–30% range. The results with the Quick test were found to be different from those in group A. Thus the number above the upper therapeutic range—i.e., over the 30% upper limit of the Quick test—was considerably higher.

Results of Thromboplastin-generation Test

The correlation between the Quick test and T.G.T. in group A was:

Test	*Good*	*Moderate*	*Poor*
Quick	7	12	12
P & P	14	6	11
Thrombotest	13	8	10

and the correlation in group B was:

Test	*Good*	*Moderate*	*Poor*
Quick	4	4	4
Thrombotest	6	2	4

Good correlation between the two tests was found in less than a quarter of the patients. The P & P test and thrombotest, on the other hand, correlated well about twice as often. But the correlation was only moderate or poor in more than half the patients. In figs. 1 and 2 examples are given of good and poor correlation between the T.G.T. and other tests.

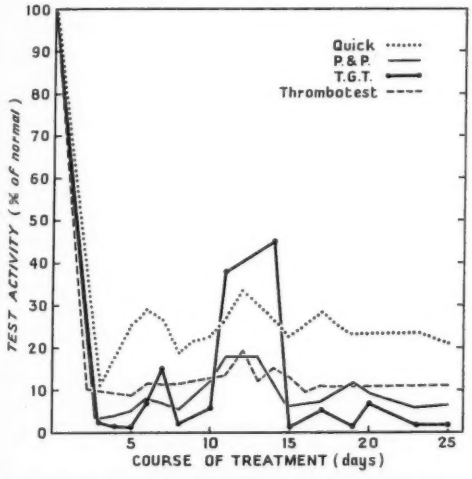

Fig. 1—Good correlation between T.G.T. and the three tests.

Good correlation was usually found when there was much depression of the coagulation factors. Thus, when the T.G.T., thrombotest, and P & P test correlated well, the Quick results were usually in the therapeutic range of 15–30%. In contrast, where the Quick test showed results above 30% activity, correlation between the T.G.T. and the other tests was relatively poor.

In nineteen of the forty-three patients a fluctuating pattern of thromboplastin generation was observed during the course of phenindione treatment. There was no obvious correlation between the T.G.T. fluctuation and the Quick prothrombin activity or the dosage of anticoagulant.

In a further six cases evidence of these fluctuations was doubtful. The remaining sixteen cases showed no evidence of " spontaneous " fluctuation in the pattern of thromboplastin generation.

A fluctuating pattern of thromboplastin generation was considered to be present if a trend was observed in consecutive tests during treatment. The results were classed as doubtful where such a fluctuation was observed only in isolated tests. Fig. 3 shows a typical fluctuating thromboplastin-generation pattern, together with the results of the Quick, P & P, and thrombotest.

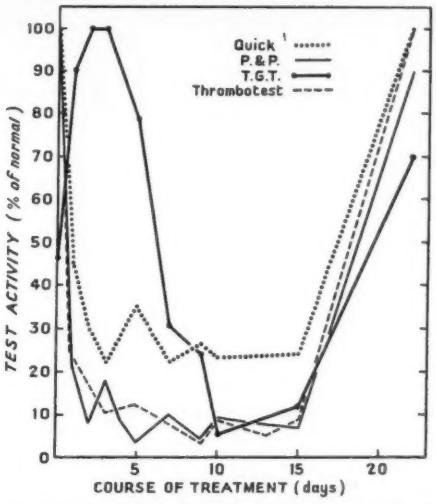

Fig. 2—Poor correlation between T.G.T. and the three tests.

In contrast the six controls (hospital patients without clinical evidence of thrombosis) gave a consistent 100% thromboplastin generation in all estimations made over a 10-day period.

The forty-one treated patients were classified into 4 groups—i.e., thrombotic (proved cases), doubtful thrombotic, non-thrombotic, and cases of angina pectoris. The presence of fluctuating thromboplastin generation patterns in these groups is seen in table II, about 50% of the proved thrombotic cases showing these fluctuations.

In eleven patients *before treatment*, the results of the T.G.T. showed that thromboplastin generation was increased—i.e., was above 100%—when compared with normal controls. Six were patients with proved thrombosis, and four had suspected but not proved thrombosis. One had angina pectoris. In all these cases the Quick test, the P & P test, and thrombotest did not reflect this increase in thromboplastin activity. In fact, in five cases thrombo-

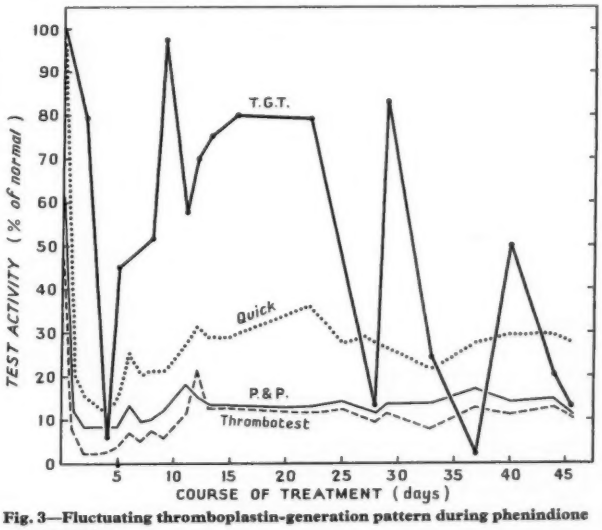

Fig. 3—Fluctuating thromboplastin-generation pattern during phenindione treatment.

TABLE II—T.G.T. PATTERNS IN PATIENTS TREATED WITH ANTICOAGULANTS

T.G.T. pattern	Cases			
	Thrombotic	Doubtful thrombotic	Non-thrombotic	Angina
Fluctuating ..	13	2	0	5
Doubtful ..	3	1	1	0
Non-fluctuating	11	7	0	0

test gave results below 100%, suggesting that thromboplastin generation was decreased.

In six patients thromboplastin generation was depressed before anticoagulant treatment had been instituted. Four of these showed depressed Quick prothrombin activity and a prolonged thrombotest, whereas only three gave a prolonged P & P test.

In twenty-one patients the thromboplastin-generation test returned to normal or near normal during the course of phenindione treatment, although the Quick test was within the therapeutic range.

The speed with which thromboplastin generation was depressed to 30% or less during phenindione treatment varied considerably. In fig. 4 the day on which such depression was first observed has been plotted for the whole series.

Thrombotest and the Prediction of Hæmorrhage

Three non-fatal hæmorrhagic episodes arose during the course of treatment of the forty-three patients—two in group A and one in group B. These incidents represent one non-fatal hæmorrhage per 8 months of short-term treatment. On each occasion the Quick prothrombin activity was still within the therapeutic range, whereas the thrombotest was below 10%, and the thromboplastin generation less than 5%. In the two patients of group A the P & P test was also less than 10% of normal.

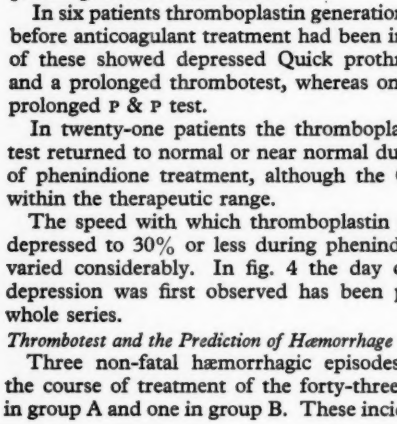

Fig. 4—Days before thromboplastin generation was first observed below 30% of normal in forty-three patients on phenindione treatment.

Death during Anticoagulant Treatment

There were four deaths—two in each group. The numbers are too small for any conclusion to be drawn.

Thromboembolic Complications

No thromboembolic episode was observed clinically in either group.

Discussion

The Quick test, first described in 1935, has been the sheet anchor for the control of oral anticoagulants since their introduction nearly 20 years ago. There have been many modifications of the test, but the basic principles have remained unchanged. The main difficulty encountered has been the standardisation of the thromboplastin extracts. Acetone-dried human brain, which has been prepared easily in our laboratory, has been found to give reproducible results. Most modifications of the Quick test are sensitive to depressions of factor VII and prothrombin, which occur during treatment with oral anticoagulants. The use of a powerful tissue-thromboplastin reagent in Quick's test makes it impossible to measure changes in factors involved in the production of intrinsic blood thromboplastin. Several workers have shown that depression of thromboplastin generation also occurs during anticoagulant treatment (Biggs et al. 1953, Hunter and Walker 1954, Koller 1954, 1955). Christmas factor and Prower-Stuart factor are involved in thromboplastin production, and both of these are reduced by the anticoagulants (Douglas 1955, Hougie et al. 1957). Changes in Christmas factor are not measured by Quick's test.

Our results relate to the Quick test performed with one particular type of thromboplastin reagent—i.e., acetone-dried human brain—the same batch being used throughout the investigation. Results with this batch were similar to those with previous batches we have prepared regularly over the past 13 years. Commercial preparations are known to give variable results owing to variable degrees of factor-VII contamination (Verstraete et al. 1957).

Hicks and Bonnin (1959) have suggested that, in the majority of patients, depression of thromboplastin generation by anticoagulants runs parallel with the depression of Quick's test, but they gave instances in which this relationship was not close. In contrast, our results indicate that only in a minority is there good correlation between the two tests. The Quick prothrombin time thus appears to be an incomplete measure of the anticoagulant effect produced by anticoagulants.

Results with the P & P test and thrombotest were slightly better, but correlation was good in less than half the cases.

Waaler (1957) showed that the P & P test was slightly sensitive to reduction in Christmas factor when low levels of factor VII and prothrombin had been attained. From our investigations we gained the impression that the P & P test and thrombotest correlate well only when these extrinsic factors are considerably depressed.

In the three cases having phenindione treatment, where there was spontaneous bleeding, the thrombotest indicated a dangerous depression of coagulability. This is important since all three had seriously impaired thromboplastin generation, although the Quick prothrombin times were within the " therapeutic range ".

In about half the patients a fluctuating pattern of thromboplastin generation could not obviously be related to the dosage of anticoagulant drug. Such fluctuations do not seem to have been reported previously. Their pattern is remarkably similar to the fluctuating coagulability pattern observed with heparin-plasma-clotting tests in patients with recent thrombosis who are not having anticoagulant drugs (Poller 1954, 1956).

Several workers have reported increased thromboplastin generation in patients with recent thrombosis (Poller 1957, MacDonald 1959, Spittel et al. 1960). Thrombotest appears insensitive to such changes in contrast to heparin-clotting-time methods, which may register a thrombotic tendency. The observation that the T.G.T. was appreciably impaired in six cases before anticoagulant therapy was commenced is of interest. In most of these cases there appeared to be a combined defect of coagulation factors, including prothrombin and associated factors.

The day on which appreciable depression of thromboplastin generation was first registered was by no means constant, varying from the start of treatment to 13 days later. This point has not been emphasised by previous

workers, although impairment of intrinsic blood-thromboplastin generation, when the Quick prothrombin time was normal or only slightly prolonged, was observed by Koller (1954) and by Hunter and Walker (1954).

Our results suggest that the therapeutic ranges of the Quick test, the P & P method, and thrombotest are not directly comparable. Either the accepted lower limit of 15% in the Quick test (using acetone-dried human brain as thromboplastin reagent) denotes too great a depression of clotting factors, or the lower limit of 10% with P & P or thrombotest is too high.

Bjerkelund (1957) and other Scandinavian workers have employed the 10% lower limit, using the P & P method, for several years, with good results—i.e., low incidence of complications. From comparison of the Quick test and the P & P method, Smith and Schelling (1955) are of the opinion that the therapeutic range with the Quick test should be 34–48% prothrombin activity.

Our results suggest that excessive reduction of thromboplastin factors may be an important factor predisposing to hæmorrhage. In our series there were four cases of hæmorrhage; in three of these the results with P & P and thrombotest were *below* the therapeutic level of 10%, and the T.G.T. showed thromboplastin generation to be below 5% of normal. In contrast the Quick test showed the prothrombin activity to be in the therapeutic range—i.e., above 15%—thus failing to give sufficient warning of possible hæmorrhage.

It is as yet too early to define exactly the therapeutic limits with the thrombotest technique. The similarity between P & P and thrombotest results suggest that the range will be 10–30%.

The chief advantage of thrombotest is that it makes available to all laboratories a simple test which gives results as reliable as the more complicated P & P test. On the other hand, there are disadvantages when it is compared with the Quick prothrombin-time test. Amongst these are the greater care necessary in collecting blood specimens, and in preparing the glassware and syringes. Although the siliconing of glassware appears simple, it is not without risks in unskilled hands. Reconstitution of the freeze-dried thrombotest reagent requires great care. One of the batches tested contained an agglutinin which gave agglutination similar to that obtained with human blood-group antibody, and this interfered with the reading of the end-point in some cases.

Since more and more patients are being treated with anticoagulants, a great disadvantage is the high cost of imported thrombotest reagent. Owren (1960) has shown that half quantities of the reagent give as reliable results and afford economy. The general principles for preparing the reagent have been described (Owren 1959), but whether such an elegant and reliable lyophilised preparation would be obtained in a hospital laboratory remains to be seen. The cost of a home-made preparation must also be appreciable. If thrombotest does give some warning of possible hæmorrhages when in fact the Quick test does not, then there is a good case for introducing the newer test at the earliest opportunity. In the meantime it seems advisable to keep the Quick prothrombin time between $1^1/_2$ and 2 times normal—i.e., 30–20% prothrombin activity—where this established test is still being used. For many years this plan has been adopted by one of us (H. L.), and it has proved satisfactory from the point of view of hæmorrhagic complications. Toohey (1958) pointed out that the P & P method was superior to the Quick method for assessing dosage at the start of anticoagulant therapy; on the other hand, for outpatient long-term therapy, where specimens were taken at fairly long intervals, the Quick method was still reliable. From our results with thrombotest similar conclusions may be drawn.

Summary

Two groups of patients having anticoagulant therapy were studied:

In group A, comprising thirty-one patients, anticoagulant dosage was based on Quick's prothrombin-time test, and simultaneous observations were made by Owren's thrombotest method, the prothrombin and proconvertin (P & P) method, and a thromboplastin-generation test.

In group B, comprising twelve patients, anticoagulant dosage was based on Owren's thrombotest method, and simultaneous observations made by Quick's test and a thromboplastin-generation test.

When group A patients were controlled by Quick's method about 30% of the simultaneous thrombotest results were below the therapeutic range, suggesting that too much anticoagulant was given.

When group B patients were controlled by the thrombotest method about 30% of the simultaneous Quick test results were above the therapeutic range, suggesting that not enough anticoagulant was given.

Among the forty-three patients there were three non-fatal hæmorrhages, and in each of these the Quick test results were within the therapeutic range whereas the thrombotest results were below the therapeutic range.

Fluctuation of intrinsic thromboplastin factors was studied during treatment.

Before the Quick test is replaced by the thrombotest in routine control of anticoagulant treatment more experience is required. Meanwhile it is suggested that safer control will be obtained if the Quick prothrombin time, using the described acetone-dried brain extract, is kept at not more than twice normal, and the thrombotest at not more than 3 to $3^1/_2$ times normal. No one-stage method is entirely safe in controlling anticoagulant treatment.

We wish to express our thanks to the following members of the Department of Clinical Pathology, Manchester Royal Infirmary, who so ably assisted us in this investigation: Miss Jean Carr, F.I.M.L.T., hæmatological technician; Dr. M. J. Lewis, registrar in pathology; and Dr. A. L. Buckley, resident clinical pathologist. We also wish to thank Prof. P. A. Owren for sending us preliminary information about thrombotest, and Messrs. Nygaard & Co., of Oslo, for a generous supply of the reagent. We are grateful to Evans Medical, Ltd., for augmenting our supplies of the reagent, and to Dr. M. C. G. Israëls for his helpful criticism in the preparation of this paper.

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CARDIAC ARREST TREATED BY ELEVATION OF THE LIMBS FOR FIFTEEN SECONDS

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FILLING the arrested heart with blood from the patient's elevated limbs can restart beating, as I have already reported (Woodward 1952). The same observation was made by Fowler (1952), and the method has been used experimentally (Stephenson 1958). Blood can be transferred to the heart by gravity by raising the limbs vertically. In states of reduced blood-volume, bandaging the limbs can help further, but experience has convinced me that, apart from this one indication, bandaging is unnecessary.

On four occasions, I have confirmed the effectiveness of this method when the chest has been open [Launceston General Hospital numbers 77082, 81204, U.R.7913, U.R.14234], thoracotomy allowing direct observation of the heart while the limbs were raised. In these four patients, mere elevation of the unbandaged limbs rapidly restored cardiac contractions. Having seen these responses, I concluded that, provided two conditions are fulfilled, raising the limbs vertically before incising the precordium could be of value. The provisos are: (1) cardiac arrest has been immediately recognised; and (2) no more than fifteen seconds are spent in the manœuvre. This method has been carried out on three occasions, and there has been no need for thoracotomy.

Case-records

Case 1.—A.B., aged 62, [U.R.1781], on March 13, 1956, was given thiopentone and gallamine triethiodide intravenously for bronchoscopy. During the operation, cardiac pulsation, seen through a bronchoscope in the left main bronchus, ceased. The anæsthetist could not detect the radial or carotid pulses, and gave intratracheal oxygen under positive pressure, but without effect. The patient's legs were immediately held vertically and, before the precordium could be incised, the heartbeat returned and the patient recovered consciousness.

Case 2.—A.C., aged 54, was admitted [U.R.8358] on Dec. 29, 1957, with severe hæmatemesis and melæna. After eleven bottles of stored blood, he was still in coma but a direct transfusion was followed by sufficient improvement to allow operation. When the stomach was opened, its wall did not bleed. The aorta was palpated immediately: there was no pulsation. The patient's four limbs were immediately held vertically and, within fifteen seconds, the pulse returned. After completion of partial gastrectomy, he recovered consciousness.

Case 3.—A.D., aged 61, was to undergo a left axillary dissection in St. Vincent's Hospital, Launceston, on Sept. 26, 1958. General anæsthesia was induced with thiopentone and gallamine triethiodide by Dr. K. S. Goulston who, soon after induction, noticed absence of radial and carotid pulses, could hear no heart-sounds, nor measure the blood-pressure. All visible parts of the skin became deathly pale and both pupils were widely dilated. The theatre sister immediately held the legs vertical, while her assistant did the same to the arms. Oxygen was given, but it is well known (Stephenson 1958) that, though necessary, this is not effective alone. Within fifteen seconds the pulse returned. Operation was postponed, and the patient recovered consciousness. Four days later the axillary dissection was performed without trouble.

Summary

In rapidly recognised cardiac arrest, the pulse has been restored within fifteen seconds of raising the limbs into the upright position—on one occasion, the legs only, and at other times, all four limbs.

Though cardiac massage is still the main method of treatment, it can at times be forestalled.

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ACUTE FERROUS SULPHATE POISONING TREATED WITH EDATHAMIL CALCIUM-DISODIUM

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THE committee on toxicology of the American Medical Association (1959) advised the use of intravenous infusions of edathamil calcium-disodium (calcium disodium versenate) in the treatment of acute iron poisoning. Since few reports have been published on the efficacy of this agent in acute iron poisoning we present the results obtained in a severe case.

Case-record

A boy, aged 2, weighing 31½ lb. (14·3 kg.), was admitted two hours after swallowing about forty 5-grain (total amount 320 mg.) tablets of ferrous sulphate. He vomited an unknown number half an hour after taking them, and his stomach was later washed out at another hospital.

On admission (10.40 A.M., Feb. 15, 1960), he was in severe shock and was unconscious. The blood-pressure was too low to record. Tetracycline was given intramuscularly; and an intravenous infusion of plasma was started at 11 A.M. Three-quarters of an hour later the radial pulse became palpable. Edathamil 0·5 g. in 400 ml. plasma was given intravenously from 12.15 P.M. to 3 P.M. During the afternoon he passed several black fluid stools and vomited small amounts of blood. The plasma-bicarbonate at 3.45 P.M. was 12 mEq. per litre, and 80 ml. *M* sodium lactate was given intravenously during the ensuing forty-eight hours. From 7 P.M. on Feb. 15 to 10 A.M. on Feb. 16, 0.5 g. of edathamil was given intravenously in 600 ml. of 5% dextrose. Consciousness gradually returned during Feb. 16, and on the following day he began to take milk drinks. The intravenous infusion was continued with 5% dextrose solution, and a third dose of 0·5 g. of edathamil was given on Feb. 17.

During the night of Feb. 17–18 he became increasingly restless, and by noon on Feb. 18 was semiconscious, with acetonic breath and twitching limbs. The liver on palpation was small and abnormally firm. Blood-pressure, blood-glucose, and plasma-non-protein-nitrogen levels were normal. A diagnosis of hepatic coma was made, milk drinks were stopped, and tetracycline was given by mouth. Plasma was substituted for 5% dextrose infusion. The first of several electroencephalograms (E.E.G.) was taken. By Feb. 19 clinical jaundice was evident; and, during the morning, four convulsions occurred. Towards evening he became easier to arouse; by the next day he was fully conscious and beginning to play with toys. From this point his recovery was rapid and sustained. Clinical jaundice had disappeared, and the liver appeared normal in size by Feb. 23.

At follow-up on April 14 the child appeared to be in good mental and physical health and no abnormality was found on clinical examination. Electrophoresis of plasma-proteins, plasma thymol-turbidity, and thymol-flocculation tests were normal.

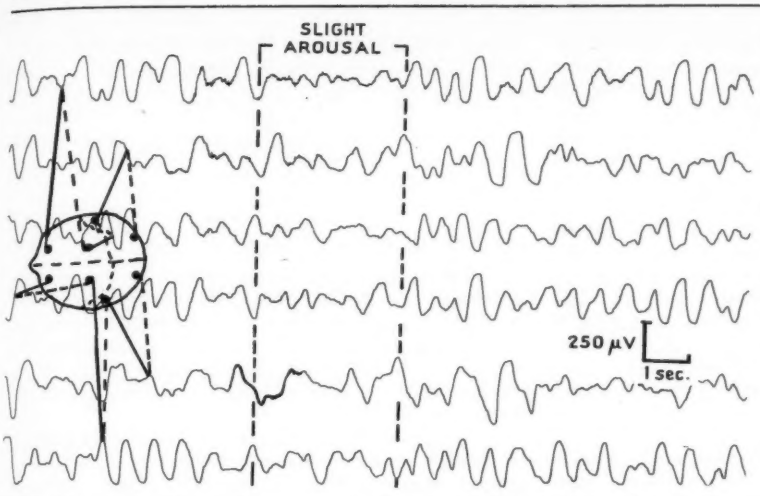

Fig. 1—Electroencephalogram from a case of acute iron poisoning, three days after admission.

Investigations

Serum-iron (μg. per 100 ml. by the method of Ramsay 1957):

Feb. 15 12.15 P.M.	6260	Feb. 16 4.30 P.M.	375
3.45 P.M.	1660	Feb. 17 12 noon	314
6.45 P.M.	1000	Feb. 18 9.30 A.M.	191
Feb. 16 9.30 A.M.	350	Feb. 22 12 noon	105

Urinary iron.—Urine was digested with nitric and perchloric acids as described by Collins and Diehl (1959). The iron content was then estimated by Ramsay's (1957) method.

No urine was passed until 7.15 P.M. on Feb. 15. From then until 5 P.M. on Feb. 17, 761 ml. urine, containing 5416 μg. iron, was passed. 3223 μg. of this total was recovered between 7.15 P.M. and 11.15 P.M. on Feb. 15.

Serum transaminase (method of Reitman and Frankell [1957]):

	Feb. 15	*Feb. 16*	*Feb. 17*	*Feb. 18*	*Feb. 19*	*April 14*
Serum-glutamic-oxaloacetic-transaminase	48	990	3400	2050	840	..
serum-glutamic-pyruvic-transaminase	25	700	2500	2400	1320	28

Other biochemical investigations.—Total serum-bilirubin: Feb. 15, 0·25 mg. per 100 ml.; Feb. 19, 4·1 mg.. Plasma-proteins: Feb. 15, 7·6 g. per 100 ml.; Feb. 20, 4·9 g.

Electroencephalography.—Six E.E.G.s were recorded. The first, taken on Feb. 18, was grossly pathological, showing large slow delta rhythms (1–2 cycles per second), up to 250 μV in amplitude, in all regions (fig. 1). The patient was then comatose, but on one occasion, when he appeared to awaken spontaneously, the delta rhythms diminished considerably in amplitude for a few seconds. The second record, taken a week later, when the patient was fully conscious though restless and irritable, showed a dramatic change. The large delta rhythms had disappeared and there was very little rhythmic activity of any kind except for occasional runs of theta waves at 6–7 cycles per second (fig. 2). Subsequent E.E.G. showed a progressive return to normal; the last record, taken on March 3, being typical of the patient's age-group.

Dr. W. Grey Walter thought the initial gross abnormality could have been due to direct specific neuronic intoxication, to a secondary disturbance of subcortical mechanisms as a result of hepatic dysfunction, or possibly to both.

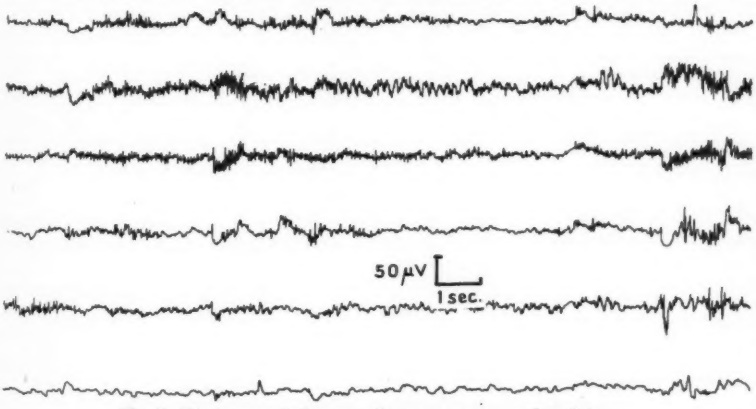

Fig. 2—Electroencephalogram of same case, seven days later.

Discussion

In cases of acute iron poisoning by ingestion it is usually impossible to determine the amount absorbed because iron lost in vomit, gastric lavage, and bowel evacuations cannot be measured. Serum-iron levels are usually regarded as indexes of iron transport, but they only indicate iron-content of the body within broad limits. Experimentally, ferric iron dialyses slowly from serum even though iron-binding protein has been saturated (Laurell 1947). In ferrous sulphate poisoning, iron leaves the blood-stream rapidly, although probably present in ferric form (Reissmann et al. 1955). Serum-iron levels in one of Spencer's cases (1951) fell from 3300 μg per 100 ml. to 1120 μg. in eleven hours. In the case reported by Brown and Gray (1955), values fell from 5450 μg. to 430 μg. in thirty-nine hours.

An estimate of total serum-iron based on the first determination made nearly four hours after the child took iron would be no more than a minimal approximation of the amount absorbed. Assuming that his plasma-volume at the time was 5% of body-weight, the plasma-iron content was 44,100 μg. In the fifty-three-hour period following the first serum-iron sampling, 5416 μg of iron, or 12% of the initial plasma-iron content, was recovered from the urine. Of the iron excreted, three-fifths was found in the first urine passed after the initial edathamil infusion, but the second and third infusions were not followed by any rise in urinary iron excretion.

Sunderman and Boerner (1949) quoted amounts ranging from 45 to 200 μg. per twenty-four hours for normal urinary iron excretion. The amount found in the urine of our patient represented a twelve-fold increase of the maximum normal figure. Increases in urinary iron excretion of the same order were found in hæmochromatosis (Figueroa et al. 1955, Wishinsky et al. 1955), hæmosiderosis (Greenwalt and Ayers 1955), and experimental iron poisoning (Foreman et al. 1952), treated with chelating agents.

Edathamil had little effect on the urinary iron excretion in our

patient although serum-iron levels fell from 6260 μg. per 100 ml. to 1000 μg. within seven hours. If the drug increased diffusion of iron from the blood, it might be valuable in the first and most critical phase of iron intoxication in which shock with hæmo-concentration develops rapidly. In rabbits poisoned with intravenous iron, shock developed within a few seconds (Brown and Gray 1955); it also appeared when animals were poisoned by intraduodenal instillation of iron in solution, a method which does not produce mucosal necrosis. This evidence suggested that circulatory changes were a direct effect of excess iron in the vascular system. If this were so, rapid removal of the excess might aid recovery from shock. The rate of fall of serum-iron in our case did not appear to be faster than that recorded by Spencer (1951), whose case received no chelating agent. Serum-iron levels in dogs poisoned with intraduodenal ferrous sulphate where higher in untreated animals than in those receiving edathamil intravenously immediately after iron was given (Bronson and Sisson 1960). Death was not prevented, however, and the amount of serum-iron did not appear to be the determining factor. The only survivor was also given disodium orthophosphate into the stomach when iron was administered into the duodenum.

The course of the child's illness followed closely the biphasic pattern emphasised by Prain (1949) and Spencer (1951). An initial period of shock, recovery from which could be attributed to the measures taken to increase plasma-volume and to correct acidosis, was followed about sixty hours later by a second period of coma. The clinical diagnosis of hepatic coma was supported by very high levels of serum-transaminase, increased plasma-bilirubin values, changes in plasma-protein levels, and normal plasma-non-protein-nitrogen values. The abnormal E.E.G. records were also consistent with this diagnosis. The second critical phase was successfully negotiated within forty-eight hours and recovery was then rapid. The same sequence of events has been reported in severe cases which were not treated with chelating agents.

Summary

A non-fatal case of acute iron poisoning in a boy, aged 2, is reported. Treatment included the use of intravenous edathamil calcium-disodium (calcium disodium versenate), and its effect is discussed. The plasma-iron content at the start of treatment was 44,000 μg. In the following fifty-two hours 5416 μg. of iron was found in the urine.

The biphasic nature of the clinical course is again emphasised. Relapse in our patient was the result of liver dysfunction.

We are grateful to the consultant physicians of the department of child health and the department of pathology, United Bristol Hospitals, for their advice and their permission to publish this case.

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CANCER OF THE ŒSOPHAGUS

PALLIATION BY INTUBATION

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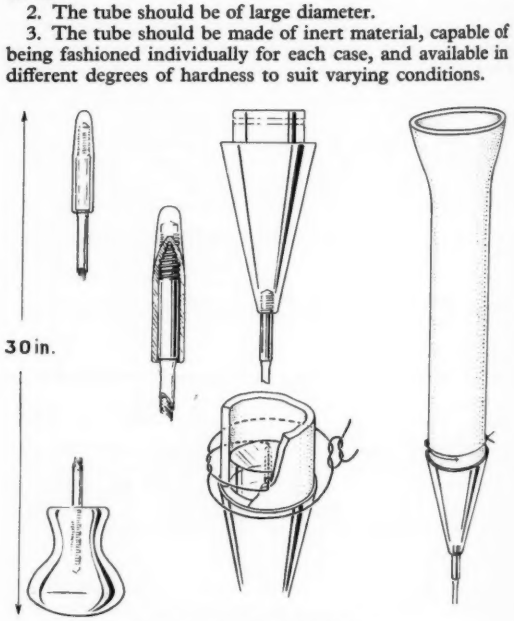
THE most important function of any palliative procedure in cases of inoperable cancer of the œsophagus or of the cardia is the relief of dysphagia. Obstruction in the œsophagus or the upper end of the stomach cannot always be relieved by radiotherapy; Souttar's tubes have certain disadvantages; and gastrostomy is a most undesirable procedure.

Recently there has been a revival of interest in methods of inserting a tube through the obstruction, either via an œsophagoscope (Weisel et al. 1959, Sachs 1959) or through a gastrostomy opening (Gourevitch 1959, Moghissi 1960).

Ideally, after intubation, the patient should be able to swallow without difficulty, and there should be no restriction in the diet. Gourevitch (1959) has summed up the main disadvantages of intubation through an œsophagoscope. We would add another to his list—namely, the size of the tube that can be passed is limited by the diameter of the lumen of the œsophagoscope. This is important because we believe that it is essential to insert as large a tube as possible, and this can only be done easily from below. The danger of splitting the œsophagus, or of hæmorrhage from the growth, has been exaggerated; it is possible to dilate a malignant stricture much more widely than is generally believed.

These points are important:

1. The method should be simple. Œsophagoscopy—particularly in the elderly patient—is not always either easy or safe.
2. The tube should be of large diameter.
3. The tube should be made of inert material, capable of being fashioned individually for each case, and available in different degrees of hardness to suit varying conditions.



The œsophageal tube introducer.

Over the past two years we have developed a method, used in 9 cases, which satisfies these requirements. Polyvinyl chloride tubes, supplied in two degrees of hardness by Portland Plastics Limited, are used. An introducer with interchangeable ends, to fit three different sizes of tube (numbers 30, 40, and 50), has been designed. A flange is made at the upper end of the tube. This can be done quite simply by immersing the end of the tube in boiling glycerin, at the temperature of which (290°C) it becomes easily malleable. It is then passed over a conical object of suitable size, and, on cooling, the splayed-out end remains a permanent flange. The introducer (see figure) consists of 30 in. of Bowden cable with a screw-threaded end, to which can be attached either a small 'Perspex' tip, or one of three perspex cones. The cable is coated with "cold-cure" 'Silastomer' (Midland Plastics Limited); this is a silicone rubber covering which is flexible and can be used at temperatures up to 200°C.

Technique

The inoperability of the tumour is determined either clinically or at operation. A high anterior gastrotomy is then made and the introducer, with the perspex tip attached, is passed up the œsophagus and delivered through the mouth by the anæsthetist. The tip is then unscrewed and the appropriate cone attached. These cones are so designed that the base fits into the lumen of the tube, while the rim of the cone, which is of slightly larger diameter than the outside diameter of the tube, does not project, and thus the tube cannot catch in the growth as it is pulled through. The tube is tied to the base of the cone by a thread, passed through the wall of the tube and through the channel provided in the base of the cone. Traction on the introducer then causes the tube to pass easily down the œsophagus, until the flange is just above the growth. The cone is then detached, and any excess of tube cut off, so that the lower end lies in the upper third of the stomach. The gastrotomy is closed.

We wish to thank the department of medical physics at the Royal Marsden Hospital for making the instrument, and Midland Silicones Limited for the supply of "cold-cure" 'Silastomer'.

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Preliminary Communication

BLOOD-CHOLESTEROL AND ASPIRIN

ARTERIOSCLEROSIS and cardiac infarction are particularly important problems at the present time. Many workers consider that there is a definite relationship between the blood-cholesterol level and arteriosclerosis. Various diets have been tried in arteriosclerotic diseases, and attempts made to lower the blood-cholesterol level by administering linoleic acid. Dreyfuss [1] observed a rise in the blood-uric-acid level in some cases of arteriosclerosis, but emphasised that the blood-cholesterol level was not invariably raised. I have noted that in some cases of arteriosclerosis not only the blood-cholesterol but also the blood-uric-acid level is raised.

On the assumption that there might be a metabolic relationship betweeen cholesterolæmia and raised blood-uric-acid levels, an attempt was made to lower the blood-cholesterol level by decreasing the blood-uric-acid. For this purpose small quantities of aspirin (1·5 g. daily) were administered to 10 patients (6 men and 4 women) whose ages ranged from 38 to 65 years. 6 of them had had myocardial infarction and 1 of these was also hypertensive; 2 were hypertensive; 1 had recurrent anginal pain; and 1 had peripheral arteriosclerosis.

BLOOD-CHOLESTEROL AND BLOOD-URIC-ACID (MG. PER 100 ML.) BEFORE, DURING, AND AFTER TREATMENT WITH ASPIRIN 1·5 G. DAILY

Case no.	Before treatment		After 2 weeks' treatment		After 1 month's treatment		After end of treatment	
	Chol-esterol	Uric acid	Chol-esterol	Uric acid	Chol-esterol	Uric acid	Chol-esterol	Uric acid
1	270	4·7	240	4·7	180	4·0	..	..
2	370	6·2	220	6·2	..	..	370	..
3	310	4·2	175	3·2	228	3·2	..	..
4	330	5·2	286	5·0	230	6·0	310	6·2
5	270	4·0	230	5·0	..	..	300	4·2
6	350	4·8	280	4·0	..	..	..	..
7	331	4·3	190	3·7	..	..	..	..
8	240	5·0	198	4·35	215	5·4	..	..
9	300	4·0	135	3·25	..	..	..	..
10	342	4·5	260	4·7	..	..	..	..

The effects on blood-cholesterol and uric-acid levels are summarised in the accompanying table.

All these patients were treated while up and about; no change was made in their usual diet or in their daily routine. After treatment with aspirin a striking fall in blood-cholesterol level, and a smaller fall in uric-acid level, was observed in all cases. In several cases, blood-cholesterol levels rose after the cessation of treatment and reverted to their original value.

I conclude that aspirin has an effect, so far unexplained, on the metabolism of cholesterol.

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1. Dreyfuss, F. *Harefuah*, 1959, **57**, 329.

New Inventions

A SUCKER FOR EMPTYING THE INTESTINE

IN cases of small-bowel obstruction it is now the usual practice to empty the intestine at operation by means of a sucker. The entire length can be cleared of fluid and gas by coaxing the instrument through successive loops of distended bowel.

Because the available sucker ends are often too short to reach the whole length of small intestine, a special long sucker

has been devised [1] for this purpose. An alternative device, developed independently about the same time, has been made for me by Down Bros., Ltd., 21, St. Thomas' Street, London, S.E.1.

This sucker consists of a brass tube 6 in. long, with threads cut at each end so that it can be used to extend the standard Poole's sucker end by simply unscrewing the outer sheath and screwing in the extension tube; there is no need to extend the inner tube. A $^1/_2$ in. flange at the proximal end of the extension tube makes it easier to use.

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1. Savage, P. T. *Brit. J. Surg.* 1960, **47**, 643.

Reviews of Books

Measurement of Subjective Responses

Quantitative Effect of Drugs. HENRY K. BEECHER, M.D., Henry Isaiah Dorr professor of research in anæsthesia, Harvard University. London and New York: Oxford University Press. 1960. Pp. 494. 102*s*.

THE main problems of therapy are to relieve, and if possible abolish, pain and to ease anxiety; and there are age-old remedies for these conditions and brand-new ones hot from the chemist's bench. The difficulty is to find the agents which work best and have the fewest disabling and harmful side-effects. This is not easy since we have little knowledge of the physiological basis of anxiety, though we all think we mean the same thing when we use the word. Again, we cannot describe pain nor compare one person's pain with that of another. A good controlled experiment demands the use of dummy drugs, and this raises a question of ethics. Should sufferers be given placebos? Dr. Beecher points to the interesting fact that the worse a patient feels the more probable is it that a placebo will help him, which seems to show that pain and anxiety render patients more suggestible. Placebos may even induce undesirable side-effects. As far as relief of pain is concerned it is possible that few drugs relieve the pain itself, but many lessen the reaction to pain; and it is the reaction which is distressing, as the response of people who have undergone frontal leucotomy or lobotomy illustrates. Pain, like all perceptions, is not pure, but contaminated by the reaction component, and it is this rather than the pain per se which differs so much from person to person, or in the same person in different conditions.

This last point raises the question of the usefulness of experimental as against clinical assays of pain-relieving drugs. In experimental conditions the human subject suffers little anxiety; he knows that the trauma is transitory and unimportant. He is, therefore, a bad experimental animal. On the other hand, the use of animals yields results which are clinically useful since to the animal the experimental threat is as great as any other and holds the same elements of anxiety. Thus, the animal and the sick man hold remarkably similar views on the efficacy of certain drugs. These are some of the facts discussed by Dr. Beecher. He has planned a number of ways in which errors of assay can be avoided and imponderables measured to some extent. He deals with pain- and anxiety-relieving substances, and a number of others affecting nausea, pruritus, cough, euphoria, sedation, and so on. He makes the interesting statement that many cough-suppressing drugs do not really reduce the frequency of cough but do reduce the patient's awareness of it. Clearly this is an important and interesting book, well worth study, especially since the methods advocated can be used for measurement of reactions, quite apart from the effect of drugs on the causes of the reactions.

The Neurological Examination of the Infant

ANDRE-THOMAS, YVES CHESNI, S. SAINT-ANNE DARGASSIES. Editors: R. C. MAC KEITH, P. E. POLANI, E. CLAYTON-JONES. London: National Spastics Society. 1960. Pp. 50. 5*s*.

THIS concise, informative, and well-produced guide to the neurological examination of the infant is published as a hard-cover supplement to the *Cerebral Palsy Bulletin*. Pædiatricians and others will be grateful for the information in this handy but durable volume because it is not readily accessible elsewhere although essential for the acquirement of the important skills required.

The first part, which deals with the neurological examination of the newborn, is based on a regional scheme which enables the examination to be carried out in a methodical well-organised way. This is described with great clarity both in words and in diagrams. The second part is concerned with the examination of older infants and has perforce to consider the evolution of each function separately. This makes it less helpful as a technical handbook, and in spite of the inherent dangers it might have been useful to include a chronological table synthesising the approximate neurological responses expected at appropriate months during the first year of life.

Medical Physiology and Biochemistry

Howell's Textbook of Physiology. 18th ed. Editors: THEODORE C. RUCH, PH.D., professor and executive officer, department of physiology and biophysics, University of Washington School of Medicine; the late JOHN F. FULTON, M.D., Sterling professor of the history of medicine, Yale University School of Medicine. Philadelphia and London: W. B. Saunders. 1960. Pp. 1232. 112*s*.

THIS is an excellent edition of an old textbook, under a new name and with an additional editor. The title attempts to summarise the aims of the book—namely, to give an account of physiology which is firmly based on the fundamental sciences, and to show how it relates to clinical problems of a somatic, nervous, or psychiatric kind. The editors have had admirable help from an array of workers each of whom is well known in his own territory. The writing is clear and the information accurate. Discussion of the clinical applications has been woven successfully into the general text and not placed separately as though clinical and scientific physiology were things apart. Many chapters have been entirely rewritten and the others drastically revised. Purely biochemical matter has been omitted. At the beginning of each chapter there is a useful summary of its contents, and at the end of each a number of references is given. This edition is a great improvement on its immediate predecessors in that the index is full and informative so that the book can be used without difficulty.

Publishers face enormous difficulties in keeping down the price of a new book, particularly one which must have many clear figures, and few of those for whom this book is written—medical students—will feel able to buy it. We may have to return to the days when books were so costly that they were chained, and lecturers revert to their original task of reading to those who sit under them.

The Urological Aspects of Bilharziasis in Rhodesia

R. M. HONEY, M.B., F.R.C.S., consultant urologist, Salisbury Hospitals Group, Rhodesia; M. GELFAND, C.B.E., M.D., F.R.C.P., consultant physician, European and African Hospitals, Salisbury, Rhodesia. Edinburgh: E. & S. Livingstone. 1960. Pp. 71. 7*s*. 6*d*.

FROM a study of 300 European and 100 African cases, the authors of this valuable book define a number of important differences from the more widely known Egyptian form of the disease and draw attention to its varied manifestations in white and coloured races. The disease is so endemic among Africans that the early symptoms are often disregarded and advice is sought only in the later stages. On the other hand, the age-incidence among Europeans at the time of diagnosis is considerably lower. This difference may in part account for the fact that no cases of carcinoma in association with bilharziasis were encountered among Europeans although in Africans they were not uncommon. Neither race, however, seems particularly prone to secondary urinary calculi. The cystoscopic appearances and radiological findings in various phases of the disease are discussed in detail and amplified by a number of well-chosen illustrations.

In the matter of treatment the authors emphasise the value of pyelography in conjunction with instrumental examination in distinguishing between the effects of ureteric obstruction and reflux and in determining the appropriate management of complications in the upper urinary tract.

Stress and Psychiatric Disorder (Oxford: Blackwell Scientific Publications. 1960. Pp. 151. 21*s*.).—The twelve papers read and discussed at the second Oxford conference of the Mental Health Research Fund provide a varied and stimulating survey of modern research into the effects of stress on men and animals. The papers on the effects of training under stress in children (E. J. Anthony), experimental neuroses in animals (Howard S. Liddell), and prevention and treatment of psychiatric reactions to stress by psychosocial means (J. D. Sutherland) deserve special mention. The editor is Dr. J. M. Tanner, secretary of the research committee of the Fund.

THE LANCET

LONDON 19 NOVEMBER 1960

New Ideas on Epidemic Virus Infections

MANY of the important epidemic virus diseases of man are transmitted directly from person to person without the intervention of an intermediate or alternate host. Of the factors which influence susceptibility, such as inherent or acquired immunity, some are quite well understood; but the factors affecting virus transmission are much less well defined. Even in such a well-studied disease as poliomyelitis it is uncertain whether virus from the throat or from the fæces is the more important. In many respiratory infections infected secretions are probably the source of the virus, but we do not really know exactly how and where the virus reaches its next host. We would expect to find that such virus infections are more readily transmitted when people live under crowded conditions, and when standards of hygiene are low; and this seems to be true for poliomyelitis and the common acute respiratory virus infections. It is well known, however, that some virus diseases tend to become epidemic in the summer and others in the winter.

ANDREWES [1] has pointed out that, although Asian influenza was seeded widely in many countries by modern means of travel, yet in most places epidemics developed only when the cold season came on. Temperature could not determine the "winter factor", for otherwise "the tropics would never get epidemics at all"; and he suggested that in winter the main change was that people were more crowded where they lived and worked—a change which applies particularly to children who go back to school in the autumn, and who often get colds then. HOPE-SIMPSON [2] found an astonishingly close correspondence between increase of outdoor temperature and decrease in the number of patients who consulted him on account of colds. In another study he showed over a three-year period in a group of volunteers that there was a similar correlation between the appearance of symptoms of colds and decrease of temperature 1 ft. below the surface of the earth. He suggested that the reason for these correlations is that in cold weather we heat our rooms and thus reduce the relative humidity of the air; and he found that switching on a one-bar electric fire in an average-size room with the window and door open reduced the relative humidity from over 80% to about 50% as the temperature rose from 20° to 30°C. This drier air, by drying the mucous membranes of the respiratory tract, may increase susceptibility to infection. WADDY [3] earlier proposed that low absolute humidity could act in this way to aid the spread of airborne disease; and one of the illustrations he used to support his view was the influenza pandemic of 1918–19. Nevertheless, when volunteers are inoculated with cold viruses at a wide range of humidities and temperatures the frequency with which colds develop does not seem to vary.[4 5]

Polioviruses, by contrast, are more prevalent in the later summer months; and the explanations of this have run on the same lines as those of changes in the prevalence of other infectious agents found in the fæces—i.e., greater frequency of fæcal-feeding flies, and the larger consumption of uncooked food. These factors must be assumed to overcome the effect of larger amounts of light and higher temperatures, which would tend to reduce the amount of surviving virus. Humidity is not generally regarded as an important influence on the transmission of polioviruses.

Laboratory experiments by HEMMES et al.[6] in Utrecht may cause us to revise our thinking, and may reconcile some apparent conflicts. These workers prepared from virus suspensions aerosols which they held in a closed system, measuring the rate at which virus infectivity was lost. Temperature and absolute humidity had little effect on this rate; but it was strongly influenced by relative humidity, and there seemed to be a sharp distinction between results obtained at a relative humidity of 40% or lower and one of 50% or higher. In the case of influenza virus (PR8 strain) inactivation of infectivity was slow in the drier conditions and over 10 times more rapid in the moister conditions. The reverse held for a strain of poliovirus type 1, which survived well at relative humidities above 50%, but which at 40% or lower was inactivated so quickly that no virus could be recovered from an aerosol 30 seconds after spraying. Experiments of this sort have many technical snags: some of the aerosol may be lost on the wall of the container, and the composition of the suspending medium or the medium in which samples were collected may greatly affect the survival of viruses. But it is very unlikely that such technical difficulties would alter the relatively greater rate of inactivation of influenza virus in humid air and of poliomyelitis in drier air. In fact the observations with influenza have been confirmed independently [7] in experiments conducted by a somewhat different technique. HEMMES et al. point to the correlation between low indoor relative humidity and increased prevalence of influenza, and between high indoor humidity and increased prevalence of poliomyelitis. Their calculations suggest that in the colder months the relative humidity indoors drops below the critical zone of 40–50% which was found in their experiments. Their hypothesis, then, is that seasonal variations in the

1. Andrewes, C. H. *J. roy. Soc. Hlth*, 1958, **78**, 533.
2. Hope-Simpson, R. E. *ibid.* p. 593.
3. Waddy, B. B. *Lancet*, 1952, ii, 674.
4. Andrewes, C. H. *ibid.* 1949, i, 71.
5. Dowling, H. F., Jackson, G. G., Spiesman, I. G., Inouye, T. *Amer. J. Hyg.* 1958, **66**, 59.
6. Hemmes, J. H., Winkler, K. C., Kool, S. M. *Nature, Lond.* 1960, **188**, 430.
7. Harper, G. L. Unpublished.

prevalence of these two virus infections result from variations in the relative humidity indoors, which in turn affect the chances of survival of the viruses in the dried state.

This hypothesis has the great virtue that it can be readily tested. Many different viruses are now known to cause respiratory disease in winter; while many other members of the enterovirus group tend, like polioviruses, to be found in summer. It should not be difficult to compare the survival of some of these viruses at high and low relative humidities with the known facts of their epidemiology, and thus to substantiate or refute this interesting suggestion.

Endocrine Exophthalmos

THE exophthalmos associated with Graves' disease is commonly of minor importance compared with the thyrotoxicosis: it is usually mild and rarely accompanied by paralysis of the external ocular muscles. By contrast, in the exophthalmos associated with exophthalmic ophthalmoplegia,[1] thyrotoxicosis is usually mild or has been relieved by treatment or replaced by frank myxœdema, but the paralysis of external ocular muscles is often pronounced and may become complete and vision may be jeopardised by secondary infection or vascular thrombosis. These two clinically different types have been termed thyrotoxic and thyrotrophic exophthalmos respectively, implying that the former results from increased secretion of thyroid hormone and the latter from increased secretion of thyroid-stimulating hormone (T.S.H.). These terms are wholly misleading since every gradation between the two syndromes can be found, the pathological anatomy is essentially the same, and there is no evidence that increased secretion of either the thyroid hormone or T.S.H. plays a major part. There is, however, experimental evidence that exophthalmos is produced more easily in the hypothyroid animal [2]—an observation which may be relevant to the severity of eye signs in exophthalmic ophthalmoplegia and their mildness in Graves' disease.

The principal agent responsible for experimental proptosis was found to be present in extracts of pituitary tissue,[3 4] and in 1953 DOBYNS and STEELMAN [5] separated the exophthalmos-producing substance (E.P.S.) from T.S.H. by differential solubility in trichloracetic acid. They tested it by its capacity to produce exophthalmos in the minnow, *Fundulus heteroclitus*. Clinical evidence in support of the experimental work has been accumulating. In 1956 two groups [6 7] described their work on the measurement of T.S.H. in serum in a total of 35 patients with thyrotoxicosis or exophthalmic ophthalmoplegia. They used different techniques, and their results at best were only semiquantitative. Both groups were generally able to detect T.S.H. in the serum of their patients: one [6] found no correlation with the degree of exophthalmos, while the other [7] found some evidence suggesting that T.S.H. might occasionally be increased with severe exophthalmos. ADAMS and PURVES [8] pointed out that T.S.H. is normally present in high concentration in the serum of patients with myxœdema and that it is suppressed by treatment with thyroid hormone. They suggested that the presence of normal amounts in the serum of thyrotoxic patients is surprising and may indicate a failure in the mechanism for its suppression—a failure that may be the cause of Graves' disease. There is no good evidence, however, that T.S.H. is the cause of exophthalmos.

In 1954 DOBYNS and WILSON,[9] using the minnow, demonstrated E.P.S. in the serum of 6 patients with exophthalmos and suggested that the degree of response in the fish was correlated with the severity of the exophthalmos. This work has been extended by MCGILL [10] using the goldfish, *Carassium auratus*, and by DER KINDEREN et al.[11] using the carp, *Cyprinus carpio*. Both groups developed reasonably satisfactory quantitative procedures and found evidence suggesting that the active principle causing exophthalmos was the same in serum and in pituitary extracts. They both examined the serum from a large series of people and detected an abnormally high level in patients with progressing exophthalmos, a normal level in those with stationary or regressing exophthalmos or with myxœdema, and a low level in those with pituitary failure. There is therefore clinical evidence to support the claim that exophthalmos is caused by increased secretion of E.P.S.

RUNDLE and POCHIN [12] and DOBYNS [13] showed that protrusion of the eyeball is the result of an increase in the bulk of the retrobulbar tissues. The amount of fat in the fat depots is much increased, and the extraocular muscles are greatly enlarged and their fat content may be doubled. DOBYNS claimed that in the laboratory animal the fat is unusually gelatinous and is infiltrated with leucocytes, lymphocytes, and tissue macrophages; and the amount of fat in the muscles is closely correlated with muscular weakness. Similar but less severe changes may affect skeletal and cardiac muscle; and large amounts of fat are found in the liver, kidneys, and epithelium besides large phagocytic cells in the lungs, spleen, and lymphnodes. Evidently the effect of E.P.S. is widespread, and indeed it is highly improbable that the pituitary gland would produce a hormone which specifically caused exophthalmos. It is more likely, as MCGILL suggests, to be a general metabolic hormone, possibly influencing water partition in fat deposits, and giving rise to ocular protrusion only when secreted in excess.

The treatment of endocrine exophthalmos has been reviewed by BRAIN.[14] No specific endocrine therapy has been proved to be uniformly effective. Œstrogens and thyroid extract have been tried extensively, but

1. Brain, W. R. *Lancet*, 1936, i, 182.
2. Marine, D., Rosen, S. H. *Amer. J. med Sci.* 1934, **188**, 565.
3. Loeb, L., Friedman, H. *Proc. Soc. exp. Biol., N.Y.* 1931, **29**, 648.
4. Shockaert, J. A. *ibid.* p. 306.
5. Dobyns, B. M., Steelman, S. L. *Endocrinology*, 1953, **52**, 705.
6. Querido, A., Lameyer, L. D. F. *Proc. R. Soc. Med.* 1956, **49**, 209.
7. Gilliland, I. C. *ibid.* p. 212.
8. Adams, D. D., Purves, H. D. *Metabolism*, 1957, **6**, 26.
9. Dobyns, B. M., Wilson, L. A. *J. clin. Endocrin.* 1954, **14**, 1393.
10. McGill, D. A. *Quart. J. Med.* 1960, **29**, 423.
11. der Kinderen, F. J., Houtstra-Lanz, M., Schwarz, F. *J. clin. Endocrin.* 1960, **20**, 712.
12. Rundle, F. F., Pochin, E. E. *Clin. Sci.* 1944, **5**, 51.
13. Dobyns, B. M. *Surg. Gynec. Obstet.* 1946, **82**, 609.
14. Brain, W. R. *Lancet*, 1959, i, 109.

there is neither physiological nor clinical evidence to suggest that these will suppress the secretion of E.P.S. Irradiation of the pituitary gland is the most logical treatment and appears to be effective in some cases; but in general the suppression of any pituitary secretion by irradiation tends to be slight and transient, as is shown by experience of this method in Cushing's syndrome. Irradiation of the orbits has its advocates, but it is difficult to establish that any improvement is not the result of accidental irradiation of the pituitary gland. Hypophysectomy or section of the pituitary stalk is apparently very effective, but is drastic[15]; and, for the present, the most reliable treatment for severe cases is tarsorrhaphy or orbital decompression.

Bathing-water

In this climate bathing is an unnatural habit and it may be for this reason that so many ills have been attributed to it. Warnings of the danger of immersion after meals, in convalescence, or when drenched with sweat are commonplaces of our folk medicine. The published evidence of infections after bathing is slight and not always convincing, but it is reasonable to distinguish between bathing in a modern swimming-bath and in natural waters fouled by unknown concentrations of human and animal excreta from all orifices. The water in a swimming bath circulates continually through a filtration and chlorination plant. It can be polluted by no-one except the bathers; and, though the degree of chlorination recommended by the Ministry of Health is not immediately bactericidal, the level of bacterial contamination is kept low.

It is possible that Weil's disease, to which Dr. Breen[16] has called attention, is the gravest danger to which the bather in natural waters is exposed. Its milder manifestations may escape diagnosis: in its more severe forms it is still often fatal. It is not a notifiable disease, but unofficial figures suggest that its incidence in England and Wales is about the same as that of typhoid fever but that its fatality-rate is higher. The leptospiræ (presumably derived from the urine of rats) can survive in water for at least a matter of hours, and experience suggests that the limpid Test is as dangerous as a source of infection as the stagnant water in an old gravel pit. Traditionally infection is most common in those who work in sewers, fishmarkets, and surface coal diggings; but today agricultural labourers are infected as frequently as any other group. It would therefore be unwise to think that bathing is the only source of infection or that, because a patient has bathed, the source of his infection is established.

Tubercle bacilli survive the ordinary processes of sewage purification and can be detected in many effluents. A few cases of tuberculosis in children have been attributed with some reason to immersion by design or accident in fresh water.[17–19] There may, of course, have been other sources of infection, but in every case the bathing site was heavily contaminated with sewage containing tubercle bacilli—and we know that the dose of tubercle bacilli needed to produce a primary infection is very small. There are other reasons too—e.g., the danger of rendering cattle who drink the water sensitive to tuberculin—which make it important that the effluents from sanatoria should be free from viable bacteria, and perhaps this has not had the attention it deserves.

Many sewage effluents contain salmonellæ, and a good deal of raw sewage and farm drainage enters our rivers without any treatment at all. The water in all our larger rivers is in fact diluted sewage, and why salmonella infections are not frequent among bathers no-one really knows. Isolated infections will seldom be reported, but not more than a dozen small epidemics have been recorded.[20] The sewage is of course diluted, but the flow of water is at its least when bathing is popular. Salmonellæ disappear rapidly from seawater by what we must in our ignorance call " natural agencies ". It may be that fresh water teeming with animal and plant life can be equally fatal. Possibly modern methods of isolating bacteria from water are so effective that they exaggerate the danger (the minimum infectious dose of many salmonellæ is 10^5 organisms or more): there is at least a hint of this in Dr. Boycott's findings.[21] Some quantitative estimation of salmonellæ in rivers might help to elucidate this problem. There are other infections which might, in theory, be acquired by bathing. Some of the earlier work on poliomyelitis in the U.S.A. suggested an association between that disease and bathing in rural areas, but other contributory factors such as fatigue could not be excluded. Today we might suspect that other enteroviruses could be spread in this way. In general, however, no association between bathing and infectious disease is so obvious as the other hazards—sunburn, traumatic damage of all kinds, and drowning. Far too many people in this country cannot swim, and it would be a pity if they never learnt because of a theoretical danger of infection.

Bacteriological standards of purity can be applied to drinking-water because its composition is more or less constant. Weather such as we have been enjoying will alter the flow of a river manyfold within a few hours and bring down silt, sewage, and dead cats in unforeseeable amounts. To make bathing safer we must use cruder methods. The main danger probably comes from the discharge of human sewage. The river boards and local authorities do their best to minimise its effects, but the work is slow and costly. Bathers in turn will do well to eschew the reaches immediately below the outfalls—if they know where these are. The council of the Society of Medical Officers of Health has been considering this problem, and has been forced to admit that it can offer no remedy other than a general clean-up. They add that their members will be unwise to press for these measures on the grounds of health. We are sure they are right: the boundaries between public health and amenity are ill defined.

15. McCullagh, E. P., Clamen, M., Gardner, W. J. *J. clin. Endocrin.* 1957, **17**, 1277.
16. Breen, G. E. *Lancet*, Sept. 17, 1960, p. 649.
17. Gaustad, V. *Acta tuberc. scand.* 1947, **21**, 281.
18. Senecal, P. *ibid.* 1950, **24**, 357.
19. Miller, F. J. W., Anderson, J. P. *Arch. Dis. Childh.* 1954, **29**, 152.
20. Moore, B. *Bull. Hyg.* 1954, **29**, 697.
21. Boycott, J. A. *Lancet*, Oct. 1, 1960, p. 760.

Annotations

WORKING WIVES—AND THEIR CHILDREN

THE shortage of teachers, nurses, and social workers is causing alarm and despondency. Each year there are fewer unmarried women, and nearly all of them already have jobs. If more women are to be found to fill the empty posts, they will be married women. Many hospitals now employ married nurses part-time, and efforts are being made under the Ministry of Education to find means of persuading married women teachers to return to their profession.

On Nov. 10 a conference was held by the National Society of Children's Nurseries entitled "Working Wives—What of the Children?" Dr. Viola Klein pointed out that, though the number of married women in employment is increasing, only a small proportion of them have young children. More than half the women in employment today have no children under the age of 16; the 1951 census showed that of the households which had children under 16, two-thirds had no child under school age; and, since the average family nowadays has less than three children, most women spend only a few years with very small children, and by the time they are 35 (or 40 at the latest) they are relatively free. The popular image of the doting mother and her two small children is unrealistic, said Dr. Klein, and seldom found. Moreover, despite increasing concern and discussion about mothers going out to work, the mother who does nothing but look after her children is in fact a new phenomenon. She is not to be found in agricultural communities. In the mid-19th century one married woman in every four had a job; moreover she had on an average 6 children and worked long hours under appalling conditions. Nowadays one married woman in three has a job, but more than half of these have no child under the age of 16.

Several speakers pointed out that we do not yet know whether the regular absence of the mother for part of the day does any harm to the child. Though working mothers are commonly blamed for juvenile delinquency, evidence is scanty; and there is no evidence at all that the effects of daily separation are comparable to the proven ill effects of total separation and deprivation.[1]

Dr. Lumsden Walker thought that whether a woman with young children should go out to work is an individual matter. Some women, unable to stand almost total isolation with young children, make better mothers if they do go out for at least part of each day. Factors which encourage a woman to go out to work are the modern small houses and labour-saving devices, increasing urbanisation with few social contacts, small families, and (in some areas) social pressures, particularly towards the purchase of "advantages"—i.e., consumer goods. Against mothers going out to work are different kinds of social pressures, and a strong and widespread feeling of guilt, often induced by "the mess of popular psychological teaching" which creates problems such as "anxiety about separation-anxiety". Also important are the attitudes of husbands and in-laws, and the availability of work.

There seemed to be general agreement that the mental health and the happiness of the coming generation depends on the love and security of maternal care; but opinions differ on what constitutes this. Many people believe, with Dr. Lumsden Walker, that stable happy parents can do more or less what they like without injuring their children's psyches, but that the situation is very different where there is instability. Anxiety and depression are probably commoner among women today than ever before, and many think that one reason for this is the social isolation of women that is characteristic of modern society. A woman has lost her previous functions as helpmate to her husband in breadwinning and as chief educator to a large brood of children, yet society imposes no demands that she seek substitute functions. She can try her hand at a paid job or at social welfare activity, but usually nobody says that she must. And so the modern wife, after her youngest child has started school, is partly functionless; which means that she is likely to question her very reason for existence and to feel a vague but pervasive dissatisfaction.[2] She may try to compensate for her own troubles with the aid of her child, but the effects of overprotection on the child are well known.[3–6]

If a mother of young children who wants to go out to work is to be either encouraged or helped, provision must be made for the children. At present, however, there are only 79 day nurseries open in the whole of London, and most of the places in them are reserved for children whose mothers are the sole breadwinners in the family. Indeed, in the whole of this country there are no more than a few places for children whose mothers work because they want to or because they feel a need to spend part of the day away from home. On the other hand, at least one local authority has now given priority to the children of women teachers, so that their mothers, much needed, can return to their profession; and in our correspondence columns this week Dr. Coghill speaks of the West Middlesex Hospital's plans for a creche-cum-nursery-school for the children of married nurses.

But there is more to the problem than this. To work full-time and also look after a house and family requires a good deal of organisation, and also stamina, both physical and mental. Naturally many women prefer to work part-time, and it has been shown [7] that wherever part-time work is to be had there is a supply of suitable workers. Many employers, however, are reluctant to employ part-timers, because these increase their administrative burden, along with compulsory contribution to insurance schemes. Moreover, absenteeism is much higher in women than in men, largely because women must stay at home not only for illness in themselves but also for illness in their families.[8]

From the standpoint of the mother, an important point is that, if she does not continue to work while her children are young, she may lose the ability to do so, and continue to be housebound and probably frustrated when her children become independent of her. In many skilled occupations and professions, including our own, failure to practise leads to loss of skill. Moreover in many professions, if one stops working, one drops out of everything: few posts are open to a woman doctor who has not practised for ten or twenty years. Lastly, even if a woman retains or regains her skill and has a chance of a suitable job, she may still

1. Bowlby, J. Maternal Care and Mental Health. World Health Organisation, 1951.
2. Rose, A. M. Mental Health and Mental Disorder. London, 1956.
3. de Leeuw, H. Woman, the Dominant Sex. London, 1957.
4. Levy, D. M. Maternal Overprotection. New York, 1943.
5. Strecker, E. Their Mother's Sons. Philadelphia, 1946.
6. Wylie, P. Generation of Vipers. London, 1955.
7. Myrdal, A., Klein, V. Women's Two Roles. London, 1956.
8. Medical Research Council: Industrial Health Research Board. Hours of Work, Lost Time, and Labour Wastage (Emergency Report no. 2. H.M. Stationery Office, 1942); A Study of Absenteeism among Women (Emergency Report no. 4, H.M. Stationery Office, 1943); A Study of Certified Sickness Absence among Women in Industry (Report no. 86, H.M. Stationery Office, 1945).

lack self-confidence. A woman who has been tied to the household for many years may find that she has an insuperable psychological block against returning to work in the outside world. Such a block is often seen in just those women who seem most frustrated by the isolation and semi-idleness of their home lives, and therefore might gain most from work.

There are many possible ways of helping to get over these difficulties. In the first place, those who advise young girls on the choice of training would do well to bear them in mind. Later, women whose children are grown up can be encouraged to use their training and experience, to revise their knowledge and practise their skills, or else to take up new training; and this would save some mothers from going out to work while their children are very young. Any drive to induce professional women to return to work would be more successful if it were accompanied by income-tax concessions: many more women would work if the cost of mother-substitutes were regarded as a legitimate expense.[9] Ashley Montagu has suggested [9] that women should have maternity leave, lasting two years, and also that married people of both sexes should work for only four hours a day. On a more immediate level, extension of the home-help system might help more women to work part-time; and, by raising the status of the domestic workers themselves, it would induce more women to take up this occupation.

These suggestions concern a number of individuals who seem to need them, and they receive publicity because society badly wants certain types of women workers. But what is even more necessary in the long run is research into the needs of women and their husbands and children.

TUMOUR VIRUSES

AT present, with the possible exception of warts, there is no known tumour virus in man; but, tumour viruses being widespread in other animals, it seems unlikely that man is in truth thus exceptional.[10] Toolan et al.[11] have described the isolation of a virus which causes a distinctive disease in hamsters inoculated as newborns or in utero (within a week before birth). The disease manifests itself in deformities consisting of small size, flattened foreface, or microcephalic domed head, protruding eyes and tongue, absent or abnormal teeth, and fragile bone structure. These deformities, previously described by Toolan[12] in her original account of the isolation of the virus, are now thought to be a late manifestation of virus infection which in higher titre causes death with lesions in the liver. The virus has been isolated from eight transplantable human tumours maintained in vivo: HEp 1, 3, 4, and 5; HS 1; HEmbRh 1; HAd 1; and A-42.[13–15] It has also been isolated from the liver and spleen of patients with cancer, but not from their tumours. The livers of rats bearing these transplantable tumours have also been found to contain the virus. Electron microscopy of infectious filtrates shows particles mainly of 70 mμ in diameter, many of which contain a nucleoid 18–25 mμ in diameter. Similar particles have been seen in the HEp 1 tumour. Cell-free filtrates obtained from four human tumours (HEp 1 and 2, HS 1, and HeLa) grown in vitro have not contained the agent. Also various transplantable mouse tumours (Crocker sarcoma 180, Ehrlich carcinoma, Bashford carcinoma, and glioma 26), three spontaneous mouse mammary tumours, the Jensen rat sarcoma, and the Walker rat carcinosarcoma failed to yield the agent. The virus has not been found—with one possible exception which is not fully described—in normal tissues from rats, mice, or hamsters.

Toolan et al. are careful to point out that there is at the moment no evidence that this new virus is a cause of the tumours from which it has been recovered. Indeed, they modestly end their paper: " While the significance of the agent in oncology is unknown, it is assumed that others will wish to know of these observations." It can be safely assumed that others will so wish and will endeavour to confirm these potentially important observations.

INTRAGASTRIC OXYGEN

NEWBORN babies commonly suffer from severe asphyxia; but most recover quickly and there is no call for treatment, apart from such simple measures as clearing the airway and keeping the child warm in the head-down position. But regular respiration is occasionally delayed for several minutes, and active resuscitation is then necessary. In the management of these cases intragastric oxygen has been used widely in this country following the original report of Akerrén and Fürstenberg.[1] The evidence in favour of this procedure is slight and mostly clinical, and recent experimental work by Coxon [2] in Oxford and Cooper et al.[3] in Newcastle has thrown doubt on its value.

In a series of experiments on cats, kittens, and puppies Coxon measured oxygen saturation in arterial and portal blood before and after gastric insufflation with oxygen. The results were compared with those obtained in a group of anoxic cats which were either not treated or had insufflation of room air. Under the conditions of the experiment Coxon was unable to demonstrate any benefits from the intragastric administration of oxygen. His findings in regard to portal blood do not confirm the claim of Poupa et al.[4] that the introduction of oxygen into the small intestine of rats raises the oxygenation of the portal hæmoglobin by 25%.

Cooper et al., in their examination of the efficacy of intragastric oxygen, found that it made no difference to the survival-time of newborn kittens deprived of intrapulmonary oxygen. In the terminal stages, when cardiac arrest was imminent, they were unable to revive kittens by means of intragastric oxygen, but were successful when the lungs were ventilated with oxygen. The Newcastle workers conclude that the average newborn kitten requires 0·30 ml. oxygen per minute for bare cardiovascular survival, but that under the most favourable circumstances no more than 0·02 ml. per minute passes from the entire alimentary tract to the mesenteric blood. Much of this oxygen will be consumed in passage through the anoxic liver, for it is likely that the ductus venosus closes functionally within a few minutes after birth. The proportion of oxygen reaching the systemic circulation must be so small as to be insignificant.

These observations relate to animals, but there has been recent confirmation from two sources of the failure of intragastric oxygen to oxygenate arterial blood in the

9. Montagu, A. The Natural Superiority of Women. London, 1954.
10. *Lancet*, 1959, ii, 277.
11. Toolan, H. W., Dalldorf, G., Barclay, M., Chandra, S., Moore, A. E. *Proc. nat. Acad. Sci., Wash.* 1960, **46**, 1256.
12. Toolan, H. W. *Science*, 1960, **131**, 1446.
13. Toolan, H. W. *Cancer Res.* 1954, **14**, 660.
14. Toolan, H. W. *ibid.* 1957, **17**, 418.
15. Skiff, J. V., Stein, A. A., Maisel, M., Heilbrunn, C., Hertz, D. *ibid.* 1958, **18**, 485.

1. Akerrén, Y., Fürstenberg, N. *J. Obstet. Gynæc. Brit. Emp.* 1950, **57**, 705.
2. Coxon, R. V. *Lancet*, 1960, i, 1315.
3. Cooper, E. A., Smith, H., Pask, E. A. *Anæsthesia*, 1960, **15**, 211.
4. Poupa, O., Kopecky, M., Chytel, F. *Nature, Lond.* 1957, **179**, 1080.

newborn infant.[5 6] There is no comparable evidence to support the claim that this is a useful procedure; and there is the further consideration that the use of intragastric oxygen carries certain risks and may delay the institution of more effective resuscitative measures.[7] The therapeutic claims for intragastric oxygen have been seriously challenged, and the onus now lies upon those who recommend its use to produce quantitative evidence of its value.

MENTAL-HEALTH RESEARCH

THE dismal facts of mental illness have been repeated so often that they have lost some of their impact. Sadly little response can now be generated by statements that nearly half the hospital beds in this country are filled by psychiatric patients, that something more than 1 person in 20 can expect to be admitted at some time to a psychiatric hospital, and that about a third of all absences from work are attributable to neurosis. And relatively little research is directed at improving this situation: the Medical Research Council, for example, put only 4½% of its total expenditure for 1959–60 into psychiatric work. Too few trained workers and not enough immediately promising lines of approach are partly to blame, but lack of money and opportunity has always been crucial.

To meet this need, a group of doctors, other scientists, and laymen started, in 1949, the Mental Health Research Fund, a charitable and independent body that collects money from wherever possible to establish research and travelling fellowships, to support specific lines of study, to organise conferences, and to award prizes. Slow at first to gain momentum, the Fund gave the first grants in 1954—a humble £3129 in that year. Growth has been steady and the annual report[8] for 1959–60 tells of £30,227 spent in research projects and of support for 25 new studies, ranging from the foster home to the effects of stress on monkeys. The total so far spent exceeds £133,000, and a great many centres in this country are conducting research sponsored wholly or in part by the Fund. The breadth of projects finding shelter beneath this wing is striking: animal ecology, the training and follow-up of the mentally subnormal, the elucidation of new syndromes, mental-hospital sociology, the psychology of brain damage: the long list shows perhaps special emphasis, however, on fundamental studies of biochemistry and neurophysiology. For the first time the Fund's report can include a substantial list of papers published by award holders, 27 in all. Support for short individual research projects, though taking most of the money, has been only one of the Fund's activities. Thus, in 1952, it organised a conference at Oxford on prospects in psychiatric research, followed by contributions to four symposia on child development at Geneva and symposia on the nervous system at Oxford, Aarhus, and Strasbourg. Seven books have emerged from these gatherings and an eighth, *Stress and Psychiatric Disorder*, just published, (see page 1124) arose from the Fund's 1958 conference.[9]

Surveying the progress of the Fund so far, Mr. Ian Henderson, chairman of the executive committee, told the annual general meeting on Oct. 31 of a new departure—a £250,000 appeal to endow permanent research posts. The Fund had become increasingly concerned with the research structure, particularly the lack of permanent prospects for those who devote themselves to this work. A "vicious circle" led to first-class men going elsewhere, to fewer applications for research appointments, and consequently to fewer research vacancies being created. Mr. Henderson noted that three branches of the Government were involved: the Minister of Health, the Minister of Science via the Medical Research Council, and the Chancellor of the Exchequer via the University Grants Committee; and therefore no one person was responsible for mental-health research as a whole. Regular sums should be set aside for the missing chairs and readerships, and an increase in voluntary support, Mr. Henderson believed, would force the State to take action.

Emphasising the dearth of psychiatric research in British universities (where it should be done), Sir Geoffrey Vickers said that only 9 university psychiatric departments existed in this country and, of these, 6 had been set up since the war. Difficulties in the early formative years, plus clinical and teaching demands, had made it very hard for these departments to conduct much research as yet; and the chair of experimental psychiatry at Birmingham University remained unfilled. Government action in promoting work of this kind was sometimes impeded by the universities' legitimate demands for independence, but Sir Geoffrey explained that the Mental Health Research Fund, as a private benefactor, could achieve this more readily by offering help to those universities that seemed most receptive. If we made an effort comparable to that in the physical sciences (including bringing in the most promising men), Prof. J. Z. Young told the meeting he believed we should soon learn how to learn, how to discover, and how to avoid those breakdowns in the brain which constitute mental illness.

A relatively small sum could transform the academic world of psychiatry; and it is no longer fanciful to hope that a breakthrough in biochemistry may release a hundred thousand people in this country from the grip of schizophrenia. The Mental Health Research Fund deserves vigorous support in its efforts to accelerate progress.

WHERE DO WE FIND MICROBES?

THE modern microbe hunter is not the pathologist trying to find the causal organism, but a teacher, student, or research-worker looking for microorganisms that are either typical and so suitable for teaching, or have particular properties such as the production of antibiotics, or depend on particular substances for growth. To find out what organisms were kept in different laboratories, and to help in the interchange of cultures, an organisation with the cumbersome title of British Commonwealth Collections of Micro-organisms was set up in 1947. With the exception of South Africa, the larger countries of the Commonwealth formed national committees which collected information and issued directories in 1951.[1]

New editions of directories covering the United Kingdom,[2] Canada,[3] India,[4] Australia,[5] and New Zealand[6] have just been published. These give the names and address of laboratories whose directors have indicated their willingness to distribute cultures to those who want

5. James, L. S., Moya, F., Burnard, E. D., Apgar, V. *Lancet*, 1959, i, 737.
6. Nelson, K. P. *ibid.* 1960, i, 317.
7. Barrie, H. *ibid.* 1959, i, 884.
8. Mental Health Research Fund Annual Report, 1959-60. 39, Queen Anne Street, London, W.1. Pp.28.
9. See *Lancet*, 1958, ii, 205.

1. See *Lancet*, 1951, ii, 1028.
2. Directory of Collections and List of Species Maintained in United Kingdom, Ghana, and Trinidad. H.M. Stationery Office. 12*s.* 6*d.*
3. H.M. Stationery Office. 9*s.*
4. H.M. Stationery Office. 6*s.*
5. H.M. Stationery Office. 8*s.*
6. H.M. Stationery Office. 3*s.*

them, and show what types of organism (algæ, protozoa, bacteria, fungi, yeasts, viruses) are kept in the different collections. The directories with their lists of species do not form a *Who's Who* for microorganisms, and, since each directory has had a different set of editors, they provide many examples of the subjectiveness of taxonomy. On nomenclature each director probably reflects the prevalent opinion of the country, but the directories should not be taken as a guide to correct usage.

The lists of species were made up from replies to questionaries sent out (in the U.K. at least) in 1958; and in a recent test it was found that several laboratories have lost or discarded some of the strains listed in that year. Furthermore, the published lists do not contain strains added since. With the reservation that the lists are not as up to date as they might be, they will still be useful to those seeking cultures. So far these lists of Commonwealth collections are the most comprehensive available. It is cheering news that plans are being made to extend the work to other countries so that a world-wide directory can be prepared.

AMBULANCES

WE have always wondered who designs our ambulances. We accept them as we accept instrument bowls and bedpans: they are not perfect but we do not know of better. Bothwell [1] has now put forward some ideas for improving the ambulance. No-one, least of all the patients, would deny the virtues which he claims for his design. Independent springing would make for smooth riding, and front-wheel drive for a low floor easy of access for walking patient or stretcher. Indeed Bothwell would go further than this: he suggests a mechanism by which the body of the ambulance could rest on the ground while it is being loaded.

Perhaps the most important lesson of this article is the small part that our profession plays in what is basically a medical (or surgical) problem. Under the Act of 1948 the ambulance services are the responsibility of the local authorities. Though nominally under the control of the medical officer of health, in many counties and county boroughs they are organised and managed by a staff which is entirely lay. We believe that every ambulance carries at least one man trained in first-aid, but the experience of some practitioners suggests that those who control the service do not always appreciate the finer points about moving sick people. Yet few M.O.H.s can afford to appoint a medical member of their staff as a full-time ambulance officer. A reasonable solution is not easy to find, but no-one must forget that in cases of doubt the medical opinion ought to override all other considerations.

If our ambulances carried emergency cases only (as they do in many parts of the U.S.A.) the organisation of the service would not be so difficult. As it is, most ambulances spend at least as much time in ferrying those who cannot use public transport to the outpatient departments. In rural districts the result is a milk round which may take up to four hours—and four hours in the best ambulance in the world is no joke if you have an ununited fracture. Wireless control of the ambulances from the control room is almost universal, and beyond doubt this makes for economy; but it is not good for the morale of a patient that while he is going to hospital the ambulance is diverted twenty miles to pick up some other unfortunate. Helicopters are expensive to buy and to run (and infernally noisy), but their use might do much for the comfort of patients. Those who have had the opportunity of seeing the type of helicopter used, and the way they were used, after the disaster at Fréjus might bring the matter to the notice of the Minister of Health.

During the late war a distinguished D.D.M.S. described the ambulance as among the most lethal weapons of war yet invented. It was certainly true on most fronts that the longer the carry the worse the prognosis. This was not only because treatment was delayed but also because in a moving ambulance the wounded man never had a moment's rest, however careful the driver and kind the attendant. In contrast, evacuation by air was peaceful and almost soporific. Our ambulances today are far grander than those used by the Army and our roads are smoother, but a journey by ambulance can be a very real ordeal for the seriously injured. Some patients stand travel better than others, but it is generally true that the faster the ride the more uncomfortable it is. There is a romantic idea still abroad that the ambulance, like the fire engine, should be subject to no traffic regulations. In this country ambulances enjoy no statutory privileges (since such privileges were withdrawn from the New York City ambulances the number involved in accidents has fallen by half [2]). On a journey of 10 miles the difference in time between average speeds of 20 m.p.h. and 40 m.p.h. is 15 minutes. It can be very seldom that this time, taken in conjunction with the times for loading and unloading, makes any difference to a patient's chances of survival. Far more often, if the vehicle travels slower the relative absence of vibration and more violent movements will be to the patient's benefit. In a study in Michigan of 2500 consecutive ambulance runs it was found that in 98·2% haste was needless and that a saving of 5 minutes would not have influenced the course of a single injury.[3] It would be interesting to see comparable figures from one of our own hospitals. The elderly practitioner who told the ambulance to come like Jehu and return like Agag gave very sound advice.

ISOENZYMES

DETECTION of increased plasma and serum enzyme activities has proved useful in the diagnosis of myocardial disease.[4 5] The changes are not specific, for they may be found also in diseases of the liver, the biliary and pancreatic tracts, and skeletal muscle. Confusion may also arise from the administration of drugs, such as the promazines, certain anticoagulants, and opiates, which may also lead to increased serum enzyme activity.

Various enzymes, it now seems, may turn out to be mixtures of several different components, called isoenzymes, which closely resemble each other in their biological activity but differ serologically and chemically, as well as in their behaviour during electrophoresis.[6 7] In different tissues, the pattern of distribution of the isoenzymes varies; and it should, therefore, be possible to recognise disease of a tissue by virtue of the fact that its isoenzyme pattern becomes duplicated in the plasma. This, of course, applies only to those diseases which result in release of tissue-enzyme content.

Particular attention has been applied by Wroblewski

1. Bothwell, P. W. *Publ. Hlth, Lond.* 1960, **74**, 459.
2. Magelaner, I., McElroy, M. *Hospitals*, 1955, **29**, 89, 172.
3. Curry, G. J., Lyttle, S. N. *Amer. J. Surg.* 1958, **95**, 507.
4. Wroblewski, F. *Ann. intern. Med.* 1959, **50**, 62.
5. *Lancet*, 1960, i, 1123.
6. Plagemann, P. G. W., Gregory, K. F., Wroblewski, F. *J. biol. Chem.* 1960, **235**, 2282; *ibid.* 1960, **235**, 2288.
7. Markert, C. L., Moller, F. *Proc. Nat. Acad. Sci., Wash.* 1959, **45**, 753.

et al.[8] to lactic acid dehydrogenase, which they have investigated by the technique of starch-gel electrophoresis.[9] This is carried out in a rectangular starch-gel, and the enzyme activity for every 0·3 cm. of the gel length can be determined by cutting out segments of appropriate size; peaks of activity can then be demonstrated at different positions along the gel. Tissue lactic acid dehydrogenase has thus been shown to consist of at least five components, referred to as LD_1, LD_2, LD_3, LD_4, and LD_5.[6] The higher the number of the component, the greater its mobility during electrophoresis. In normal human plasma, the LD_4 activity is slightly greater than that of LD_5, and these two are the major components; there are apparently sometimes four [6] and sometimes five [8] isoenzymes. Extracts of heart muscle contain the same two major components, but LD_5 predominates over LD_4. In liver tissue LD_1 predominates. In skeletal muscle, too, LD_1 predominates, but an appreciable amount of the other isoenzymes is present. Spleen shows a preponderance of LD_2 and, to a lesser extent, of LD_4. Kidney shows a preponderance of LD_5, LD_4, and LD_3, in that order. Characteristic patterns are also obtained with human pancreas and human lung; in fact, each tissue so far examined seems to have a special distribution of these isoenzymes.

In the diagnosis of myocardial infarction some of the limitations of plasma-enzyme estimation should be overcome by measuring the plasma-isoenzyme pattern of lactic dehydrogenase activity. Diseases of the liver, skeletal muscle, biliary tracts, lung, and other organs cause changes in the pattern which are characteristic of the organ or the pathological process, or both, but are not similar to those found with myocardial infarction. The plasma-isoenzyme pattern characteristically associated with myocardial infarction should reflect myocardial necrosis more distinctly than the plasma-enzyme tests previously used. The abnormal pattern can be recognised even though the plasma-enzymes are within normal limits, and it persists appreciably longer than does, for example, the rise in serum-transaminase.

Isoenzymes, besides those of lactic acid dehydrogenase, are being investigated in several laboratories; and this exciting new development points very strongly to the possibility of a kind of "finger-print" diagnosis by examination of a patient's serum. In this way, in the not too distant future, it may be possible to demarcate, with some certainty, disease of an organ or organs.

SPECIFIC MESENTERIC LYMPHADENITIS

"MESENTERIC adenitis" is an all-too-handy diagnostic rag-bag for ill-defined and evanescent disorders. As with most obscure infections, a viral origin has been suggested, but no virus has been identified. Aird[10] noted that 37 cases were admitted to a children's hospital in a period when admissions for appendicitis numbered 83. The disease is therefore quite common; and if it could be diagnosed without laparotomy many patients could be spared operation. Taylor[11] has lately reported 49 cases.

Continental workers showed that mesenteric adenitis may arise from infection with *Pasteurella pseudotuberculosis*. Knapp[12] reported 117 such cases observed in 1954–57. Most were diagnosed on serological evidence, but the causal organism was isolated from the lymph-nodes in 13 cases and from blood in 2 others. The first report from this country seems to be that of Mair et al.,[13] who, in a thorough investigation of 17 cases of mesenteric lymphadenitis, found evidence of pasteurella infection in 3. The material examined consisted of appendix, fæces, throat-swab, serum, and, in all but 5 cases, excised mesenteric lymph-nodes. The nodes and appendices were examined bacteriologically and histologically; the sera were titrated for antibodies to *Past. pseudotuberculosis*; and the fæces, throat-swabs, and nodes were cultured for viruses on amnion and monkey-kidney cells. No virus was isolated; but antibodies to *Past. pseudotuberculosis* were found in 3 cases, and in 2 of these the organisms were cultured from the lymph-nodes.

Past. pseudotuberculosis is a short gram-negative bacillus closely related to the plague bacillus and is most often found as a parasite of small rodents—particularly guinea-pigs and rats—but it has been recorded occasionally in domestic animals and birds. The specific name derives from the appearance of the lesions caused, which macroscopically resemble those of tuberculosis. Little is known of the natural spread of the disease; but animals may be infected experimentally by feeding, and the site of the lesions suggests infection by the intestine. Infections in man are especially common in winter, perhaps because of an adverse effect by cold on the animals which provide the reservoir.

The 3 British cases were subacute infections diagnosed clinically as appendicitis, although in 1 the possibility of mesenteric adenitis was considered. Agglutinins, present to titres of 1 in 300, 500, and 3000, would have suggested the diagnosis in each case had the sera been tested before operation; but the detection of antibodies during an attack is only presumptive evidence of ætiology, and the surgeon may still consider laparotomy advisable.

Mair et al. recommend culturing at 22°C as well as at 37°C. One of their isolations would not have been made without this precaution. Misleading serological reactions seem to be rare; Knapp found none in children with typical appendicitis or in over 1000 sera collected for Wassermann reactions. Two uncommon types of *Past. pseudotuberculosis* share antigens with salmonellæ, and it is therefore occasionally necessary to carry out agglutinin-absorption tests to verify the serological diagnosis. In uncomplicated cases antibodies do not persist for more than a few months. Gross and microscopical appearances of the mesenteric nodes may suggest the diagnosis, but these appearances do not have the certainty of bacteriological evidence.

Pseudotuberculosis due to pasteurellæ is found chiefly in those aged 2–5 and 12–23 years; boys are much more commonly affected than girls. Occasionally the disease assumes a septic form with typhoidal symptoms and a high mortality. In mild cases no specific treatment is needed, though, even in such cases, it may be advisable to use chemotherapy when serum-antibodies persist at a high level. Experiments by Knapp suggested that streptomycin or the tetracyclines were the antibiotics of choice. The British strains were sensitive in vitro to these drugs and also to chloramphenicol, polymyxin, neomycin, and nitrofurantoin, but were resistant to penicillin, erythromycin, oleandomycin, novobiocin, bacitracin, and sulphafurazole.

8. Wroblewski, F., Ross, C., Gregory, K. *New Engl. J. Med.* 1960, **263**, 531.
9. Smithies, O. *Biochem. J.* 1955, **61**, 629.
10. Aird, I. *Brit. med. J.* 1945, ii, 680.
11. Taylor, J. B. L. *Brit. J. Surg.* 1960, **48**, 178.
12. Knapp, W. *New Engl. J. Med.* 1958, **259**, 776.
13. Mair, N. S., Mair, H. J., Stirk, E. M., Corson, J. G. *J. clin. Path.* 1960, **13**, 432.

Special Articles

STERILISATION OF RADIUM NEEDLES AND GYNÆCOLOGICAL APPLICATORS

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STERILISATION procedures have recently undergone careful scrutiny and in many instances deficiencies in present methods have been demonstrated (Howie and Timbury 1956, Nuffield Provincial Hospitals Trust 1958). Boiling does not guarantee sterility and is open to abuses (Nuffield Provincial Hospitals Trust 1958), and Perkins (1956) has suggested that it should not be used as a sterilisation process if more reliable methods such as pressure-steam sterilisation are available.

At present radium needles and gynæcological applicators are boiled before use, and to replace this method by the use of a conventional pressure-steam steriliser would raise difficulties, because the lead necessary to provide complete protection from the gamma-radiation of the radium that might be used for only one patient would weigh 100 lb. or more.

The Investigation

It was decided, therefore, to investigate the possibility of sterilising radium needles and gynæcological radium applicators in a domestic pressure-cooker (fig. 1). This container has the advantage that it is so small that the major part of the protective lead screen can be placed around it, and only the small lead block in which the radium needles are to be carried to the radiotherapist need be placed inside.

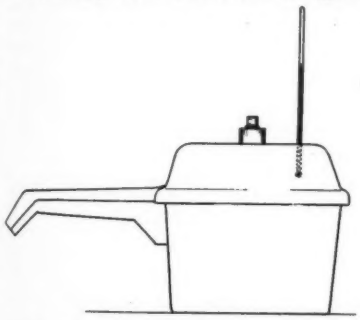

Fig. 1—Pressure-cooker used in this investigation. A thermometer was inserted through the safety plug.

MATERIALS AND METHODS

Radium containers.—Dummy radium needles were made from stainless-steel rods. They were longer than real needles to facilitate their removal from the lead blocks under test, and they were also of greater diameter (3 mm. as compared with a maximum diameter of 1·95 mm. for radium needles). Dummy inserts for ovoids were also made of stainless steel. Before being used in experiments the rods were coated with spores of *Bacillus stearothermophilus*.

The spores.—These were prepared by a modification of the method described by Alder and Gillespie (1957). The spores used in the majority of experiments, when tested on filter-paper strips, survived 4 but not 10 minutes' exposure to steam at 121°C (15 lb. per square inch). After being exposed to steam, test-spore papers were cultured in 1% glucose-peptone water at 60°C. Dummy radium needles were similarly cultured after they had been heated in the various experiments. Unheated positive controls were included in all experiments whether with spore-papers or dummy radium needles. Tests were read when these positive controls showed growth with the production of acid. This usually happened after overnight incubation. Incubation of heated spores for periods of up to 18 days beyond the time when the positive controls showed growth did not increase the number of positive cultures obtained.

EXPERIMENTAL STUDIES

Radium Needles

Preliminary experiments showed that it was not possible to sterilise dummy radium needles in a pressure-cooker if they were placed in the lead block normally used for holding them during boiling. This block had blind-ended holes for holding the needles and as air removal in a pressure-cooker depends upon turbulence it is probable that failure to sterilise was due to air being trapped in the small space between the needles and the sides of the holes in the block.

Fig. 2—Modified rectangular lead block with holes drilled right through the block and a metal plate below the block to support the needles.

To overcome this difficulty a modified rectangular lead block was designed (fig. 2). Holes 5 mm. in diameter were drilled right through the block. 2 mm. below the block a metal plate was attached on which the needles rested. This design of block had the advantage that the active part of the radium needle (which occupies the central part of the needle to within 5 mm. of each end) was still screened laterally but steam could circulate freely through the holes. The base plate was not perforated.

Experiments were conducted to find out: (1) whether the needles could be sterilised in the block; (2) whether the block impeded sterilisation as judged by comparing the sterilisation of needles outside and needles inside the block; and (3) whether needles heavily contaminated with blood could be sterilised in the block.

Results

Sterilisation of spore-coated needles.—The results of experiments with the modified block are shown in table I. In these experiments the dummy needles were heated for two different times at 121°C, the block being placed upright in the pressure-cooker. Heating for 10 minutes sterilised most of the needles, and heating for 15 minutes sterilised all of them. Spores of the same batch, tested on filter-paper strips, were killed by being steamed at 121°C for 10 minutes but not for 4 minutes.

Experiments comparing the sterilisation of needles inside the block with those lying free.—In these experiments the dummy radium needles were coated either with spores or a mixture of horse-blood and spores. The needles outside the block lay on a sheet of wire gauze above the level of the water in order to avoid any possible washing-off of the spores by the boiling

TABLE I—STERILISATION BY STEAM AT 121°C OF DUMMY RADIUM NEEDLES COATED WITH SPORES OF *B. stearothermophilus*

Minutes at 121°C	No. of needles showing survival of spores	Total needles in test
10	3	17
15	0	30
0 (unheated controls)	33	33

water. The results of experiments where the needles were heated at 121°C for 10 minutes are shown in table II.

This particular time of exposure to steam at 121°C was chosen because it was known that only a proportion of the needles would be sterilised and thus any impairment of sterilisation by the block would be obvious. It is apparent that the block did not interfere with sterilisation of the needles.

Effect of the presence of blood on the sterilisation of radium needles.—In the absence of full remote-handling facilities, washing radium needles presents a hazard to the radium handler and needles may not always be cleaned thoroughly. To assess the effect of blood-contamination on the sterilisation of needles a mixture of one part of horse-blood to three parts *B. stearothermophilus* spore suspension was made. Needles were coated with this mixture, then dried. The effect of blood on the

TABLE II—EFFECT OF LEAD BLOCK UPON STERILISATION OF DUMMY RADIUM NEEDLES BY EXPOSURE TO STEAM AT 121°C FOR 10 MINUTES

Needles coated with	Needles inside block	Needles outside block	Unheated controls
B. stearothermophilus spores only	7/41 (17%)	4/25 (16%)	20/20
B. stearothermophilus spores and horse blood ..	13/25 (52%)	8/15 (54%)	10/10

Numerator = needles showing survival of *B. stearothermophilus* spores.
Denominator = total number of needles in test.

sterilisation of these needles is clearly shown in table II. Whereas approximately five out of every six clean needles were sterilised after 10 minutes at 121°C, only half of the blood-coated needles were sterilised. All of 30 blood-coated needles were sterilised after exposure to steam at 121°C for 15 minutes whether they lay inside or outside the block.

These experiments show that dummy radium needles when coated with heat-resistant spores and blood can be sterilised in a block of the general design illustrated in fig. 2. The block used for these experiments does not, however, provide the maximum desirable protection against radiation for the person who has to carry it from the lead-screened pressure-cooker to the user.

With the aid of Mr. T. McAinsh, B.SC., of the Western Regional Physics Department, an improved block was designed. This cylindrical lead block (fig. 3) is 10 cm. in diameter and 6 cm. deep and weighs approximately 5·5 kg. (12 lb.). It will hold 24 needles in holes 5 mm. in diameter. When fully loaded, the radiation level at the centre of the block surface is 3 röntgens per hour and at 15 cm. from the block is 1 röntgen per hour. Because this block will be handled with long tongs and for very short periods only, it provides a good margin of safety.

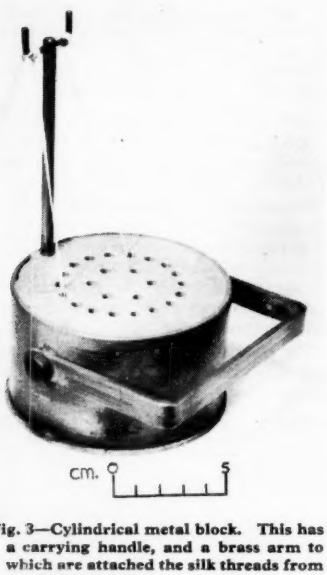

Fig. 3—Cylindrical metal block. This has a carrying handle, and a brass arm to which are attached the silk threads from the radium needles.

As there is considerably more lead in this block than in the modified block used for most of the experimental work, a perforated base plate was introduced to ensure good steam circulation through, and air removal from, the block. It seemed possible that the increased mass of lead would take so much heating that the temperature within the block might lag behind that in the rest of the pressure-cooker thus interfering with the sterilisation of needles within the block. Thermocouples placed both in the holes in the block and also in a blind-ended hole in the block have failed to show any such temperature lag.

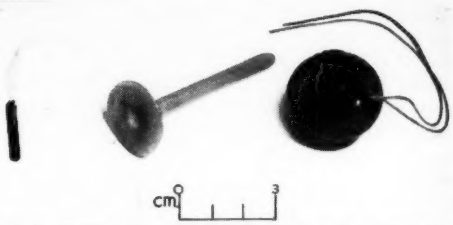

Fig. 4—Radium container, rubber cavity tube, and ovoid.

Experiments comparing the sterilisation of needles outside and inside the block have shown that 10 of 55 (18%) needles inside the block showed spore survival after exposure to steam at 121°C for 12 minutes as compared with 10 of 48 (21%) needles outside the block. These results suggest that the block does not interfere with sterilisation. (12 minutes' exposure was used here as these spores were more heat-resistant than those used for the experiments shown in table II).

Gynæcological Applicators

The other radium sources considered in this study were those used in gynæcological work for the irradiation of the cervix uteri. These are of two kinds: (1) those contained in a rubber ovoid for irradiation of the vaginal vault; and (2) those contained in a rubber intrauterine tube (fig. 4). Normally both these types of applicator are boiled before use.

TABLE III—STERILISATION BY STEAM AT 121°C OF GYNÆCOLOGICAL RADIUM APPLICATORS CONTAMINATED WITH *B. stearothermophilus* SPORES

Container	Minutes at 121°C	Number showing spore survival/ total tested
Ovoid	15	1/6
Uterine cavity tube	15	1/14 (2/14)*

* Showing growth after opening tube and culturing metal insert.

The cavity tubes were made up as illustrated in fig. 5, the metal insert being coated with spores of *B. stearothermophilus*. After being heated in the pressure-cooker, cavity tubes were cultured intact for 24 hours; then the metal inserts were removed and the tube and insert were cultured together for another 24 hours. Unheated controls included in each test revealed that some batches of cavity tubes contained a substance or substances which inhibited the growth of *B. stearothermophilus*. It was found that repeated boiling of the tubes removed this inhibitor. All tubes from "toxic" batches used in these experiments were tested, therefore, for an inhibitory effect both by incubating them in peptone water inoculated with *B. stearothermophilus* and by boiling them with the spore-coated metal insert inside and then culturing the metal insert to see if any "toxic" effect was evident only on heating. Despite the lack of toxicity eventually shown by these tests on tubes which had been repeatedly boiled, the inserts were latterly incubated alone.

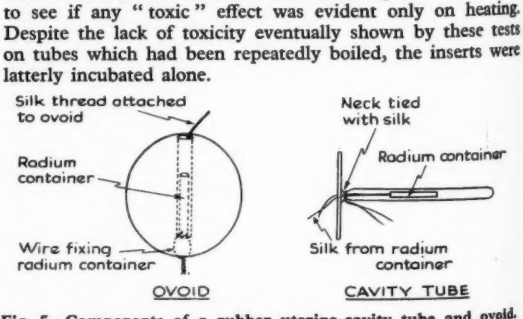

Fig. 5—Components of a rubber uterine-cavity tube and ovoid. Only one radium container is shown in the uterine-cavity tube. Normally this tube would be filled with two or three containers.

TABLE IV—EFFECT OF VARYING CONDITIONS UPON THE STERILISATION OF GYNÆCOLOGICAL APPLICATORS BY EXPOSURE TO STEAM AT 121°C FOR 15 MINUTES

Container	Conditions	Number of containers showing spore survival/ total tested
Ovoid.. ..	Placed above water	5/11
	Immersed	1/12
Uterine cavity tube	Packed with dry metal insert	0/22 (unheated controls 4/4)
	Packed with moistened insert	0/22 (unheated controls 4/4)

Ovoids and their inserts were coated with spores of *B. stearothermophilus* or with a mixture of spores and blood and were then dried. After heating, ovoids and inserts were cultured in 1% glucose-peptone water at 60°C. No evidence of a " toxic " effect was noted in experiments with ovoids.

Results

When cavity tubes and ovoids were heated above the level of water in the pressure-cooker, not all of them were sterilised by exposure to steam at 121°C for 15 minutes (table III). This may well have been due to air pocketing in, and consequent failure of steam penetration into, both the cavity tubes and the central cavity of the ovoid. Experiments were, therefore, carried out with the cavity tubes to see whether moistening the insert before placing it in the cavity tube would help to overcome this difficulty. As may be seen from table IV the results were equivocal.

Air pocketing in ovoids can be overcome by immersing them in the water in the pressure-cooker. Table IV shows the results of experiments comparing the proportion of ovoids sterilised when heated above the water in the pressure-cooker with the proportion sterilised when the ovoids were immersed in water. It may be seen that immersing them during sterilisation increased the proportion of ovoids sterilised by heating for 15 min. at 121°C.

One ovoid immersed was not sterilised after 15 minutes at 121°C. This is not surprising in view of the difficulty of sterilising the tracks through which the wire securing the radium container to the ovoid passes and those through which the silk thread passes.

In subsequent tests with metal inserts coated either with blood and spores, or with spores alone, all of 68 ovoids failed to show spore-survival after heating for 20 min. at 121°C in the water in the pressure-cooker. This result was due to sterilisation and not simply to a dilution effect, because ovoids boiled in the water in the cooker for 20 minutes showed growth of *B. stearothermophilus* on culture.

Discussion

These experiments show that it is possible to sterilise dummy radium needles within a pressure-cooker. As real radium needles are thinner than the dummy needles they will allow easier access of steam into the holes in the block with presumably still greater efficiency of sterilisation. The block described is the largest size that would be needed for one patient. Smaller blocks of a similar design could be used for smaller numbers of needles. It is surprising that inserts in uterine-cavity tubes can be sterilised, because in these tubes conditions for steam sterilisation would seem to be poor. Ovoids required heating for 20 minutes at 121°C to ensure their sterility, perhaps because of the various tracks through the rubber where steam penetration may be difficult. Since the spores used in these experiments were more heat-resistant than those of pathogenic bacteria, an additional safety margin is introduced.

To ensure that sterilisation is accomplished, a few simple precautions should be taken. The eyes of needles and other radium containers should be kept clean, perhaps by treatment in an ultrasonic instrument-washer to avoid handling problems, so that bacteria are not buried in a protein coagulum and protected from access of steam. Ovoids should be immersed in water in the pressure cooker and radium containers should be moistened before being placed in uterine-cavity tubes. It is essential, in order to remove all the air, that steam be allowed to flow freely from the pressure cooker for at least 2 minutes after the water boils, and before placing the weights on the steam outlet. If this is not done the correct temperature will not be reached inside the cooker. All articles should be steamed for 20 minutes at 121°C (i.e., 15 lb. per sq. in.). Care must be taken to ensure that the cooker does not boil dry in view of the possibility of damage to the radium containers.

By using these methods the provision of sterile radium needles and gynæcological applicators becomes a simple but sure procedure without raising major handling problems. The radium sources are placed in the pressure-cooker (which could, if necessary, be carried from hospital to hospital) on an electric hotplate which lies behind a screen of lead bricks in a room next to the operating-theatre. Ideally there should be a communicating hatch between the operating theatre and the room in which the radium is to be sterilised so that the complete pressure-cooker, after being returned to atmospheric pressure, may be pushed into the theatre on to a lead-screened table. If this is not possible the pressure-cooker could be transferred to a trolley (suitably screened with lead) and thus brought into theatre.

Once in the operating-theatre the cooker can be opened when its contents are needed and the lead block (for radium needles) or the gynæcological radium may be carried with long tongs to the radiotherapist.

Summary

A simple method of sterilising radium needles and gynæcological applicators in a domestic pressure-cooker is described. Details are given of a modified lead block which ensures adequate circulation of steam round the needles. The necessary equipment is inexpensive and the amount of protective screening is reduced to a minimum.

I am grateful to Dr. A. A. Charteris, Director of Radiotherapy and National Radium Centre, Western Infirmary, and to Dr. Mary A. C. Cowall of that department for many helpful discussions. The prototype lead block was made by Mr. A. MacDonald. The final model was made by the Western Regional Physics Laboratory. The photographs are by Mr. G. R. Kerr and the drawings by Mr. R. Callender.

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". . . In 1958 world population was 2852 million; the annual rate of increase is 1·7 per cent, far higher than it has ever been before. Unless birth-rates are reduced, many nations of Asia will be unable to achieve an economic break-through from a state of underdevelopment and underemployment to a developed and developing economy. This is because the demand for servicing the additional population will make it impossible to provide adequate finance for industrialisation and technological development. . . . Whatever can be done about food production, in Africa for instance, can only help for a very few years, if the present rate of population increase continues. Even if you could keep food production sufficiently high to feed the net yearly increase in population (which is doubtful), it is impossible at the same time to catch up with the lag of undernourished human beings, who constitute two-thirds of the people of the world."—Sir RUSSELL BRAIN, Dr. JULIAN HUXLEY, *Times*, Nov. 10, 1960, p. 13.

THE PUBLIC'S HEALTH IN 1959

Chief Medical Officer's Report

"THE country enjoyed a superb summer, beginning in May and ending in early October, and without parallel since 1911 . . . the total general rainfall in England and Wales was the lowest of any comparable period since before 1870, and probably since 1750." Memories clouded by more recent events may not readily recall the year—1959—and, in his annual report [1] on the Year of the Sun, Sir John Charles, chief medical officer of the Ministry of Health, records some other satisfactory developments and others more disquieting, notably the frightful toll of road accidents in young adults. Some items in the report are summarised below:

VITAL STATISTICS

In 1959 the *birth-rate* was 16·5 per 1000 population, thus continuing the rise that started in 1956; but the rate of increase was slackening ("it is possible that the peak in the upward swing has now been, or soon will be, reached").

The *death-rate* of 11·6 per 1000 was slightly lower, due to a slight fall in the male death-rate. Above 25 years of age the death-rate fell in all age and sex groups. Below that age, however, although there were individual exceptions, the general trend was upward. Numbers of deaths in the lower ages were now small. The increase in the male death-rate between 15 and 24 years of age was almost entirely accounted for by the increase in the number of deaths in motor accidents, which in 1959 accounted for 41% of all deaths in males between these ages.

The *expectation of life* at birth had scarcely changed since 1954, and, the report adds, it looked as though the psalmist's estimate of threescore years and ten was going to keep fairly near actuality for a number of years to come.

There was a further increase in the number of deaths from *cancer of the lung* and little sign of any slowing in the rate of increase. *Leukæmia* also showed a further slight increase.

Although the number of deaths assigned to *coronary disease* was greater than in previous years, there was a considerable reduction in the number assigned to other forms of heart-disease, which more than compensated for this. How much of the increase in coronary disease was real and how much the result of better diagnosis did not appear to be capable of ascertainment at the moment.

Deaths due to *motor accidents* numbered 6026, nearly 600 more than in 1958, and deaths from *suicide* totalled 5207, the lowest figure since 1955.

With 750,000 births (live and still) in England and Wales only 243 women died from the effects of pregnancy and child-bearing, a maternal-mortality rate of 0·32 per 1000 total births, compared with 0·35 in 1958. The infant-mortality rate was 22·2 per 1000 live births, the lowest figure ever recorded in this country.

INFECTIOUS DISEASES

"1959 will be noteworthy as being the first year in which there has been no death ascribed to *diphtheria* in England and Wales since separate identification of the disease as a cause of death was instituted in 1859" (only 18 years ago there were over 2500 deaths annually). But the number of notified cases of diphtheria again rose, and the general position regarding immunisation could not be regarded as being entirely satisfactory. The immunisation index for children under five (56·3) was still low (although steadily rising) and the importance of giving a reinforcing dose of diphtheria prophylactic to children about to enter school was still as great as ever.

A striking change has come over *whooping-cough* figures in the past two years. In 1959 notifications totalled 33,252 with 25 deaths, compared with 85,017 notifications and 88 deaths in 1957. All save two of the local health authorities now provided immunisation against whooping-cough.

The *influenza* of 1958–59 was noteworthy for two reasons; its unusually late appearance and the coexistence of outbreaks due to two distinct types of virus. Death attributed to influenza totalled 7862, of whom 5661 were aged 65 and over. On the use of influenza vaccines the report comments: "In order to effect a material reduction in morbidity from influenza it would be necessary to offer protection on a wide scale. This may well be indicated under the threat of an impending epidemic, but it is doubtful if such a course would be justifiable as a regular preventive measure in the absence of evidence of a longer period of immunity following vaccination than obtains at present." Throughout 1959 vaccination against influenza was available under the general medical service and it was left to practitioners to decide whether or not it was "desirable in an individual case".

The incidence-rate of *poliomyelitis* in 1959 was 2·3 cases per 100,000 population, the lowest reported rate since 1946. The number of corrected notifications (1028) was 800 lower than in any year in the 1947–58 period.

Sir John Charles remarks that "the story of the national campaign of vaccination against poliomyelitis is again a record of magnificent achievements by the local health authorities. . . . There is little doubt that a substantial protection is conferred by the course of vaccination now recommended".

The number of *food-poisoning* incidents (7846) was 546 more than in 1958 and showed once again that effective measures in this direction have yet to be taken. At least 17,500 persons were affected, but this total was probably far less than the real number. 75% of these outbreaks traced to a specific food were associated with such processed and made-up meats as stews, reheated meat, meat pies (mainly beefsteak and shepherd's pies), cold meat, and the like. The problem of contamination of meat required closer study before effective control measures could be taken.

The number of cases of early infectious *syphilis* treated for the first time at the clinics during 1959 showed a distinct rise, although the total remained small. The number of new patients suffering from late syphilis continued to decline. Newly diagnosed cases of *gonorrhœa* rose by 12% to 31,344, the highest level since 1947. "It seems likely that several factors are responsible for the continuing serious increase in gonorrhœa. A large number of tests so far confirm the reports that some strains of gonococci are showing an increased resistance to penicillin; in spite of good advice at the clinics and propaganda in newspapers and on television, a considerable proportion of patients discontinue attendance when symptoms are relieved thought they may still be harbouring latent and transmissible infection; in large centres of population immigrants living in difficult social circumstances still contribute greatly to the high prevalence of gonorrhœa and are particularly prone to multiple infections; and there is evidence of an increasing number of infections resulting from promiscuity among young people."

Deaths from all forms of *tuberculosis* numbered 3854, a decline of 14% from 1958. "A steady determined pressure on the disease may further reduce its incidence and ultimately bring it under complete control."

MENTAL HEALTH

The number of statutory patients under care in mental hospitals vested in the Minister and designated under the Lunacy and Mental Treatment Acts (other than accommodation designated for the reception of observation cases under the Lunacy Act, 1890) was 43,064 fewer at the end of 1959 than at the end of 1958. In the main this drop was due to the fact that from Oct. 1, 1959, it had been permissible to admit patients to this accommodation without legal formality. At the end of 1959 there were 34,173 such "informal" patients.

"The statistics of mental health and the early acceptance of the Mental Health Act of 1959 mark the pattern of change which is occurring in psychiatry, a process not yet complete and likely to change still more. Reinforcing this evidence of change is the continuing fall in the number of patients in residence despite a higher admission rate. It is hoped that with the increasing practice of both preventive and therapeutic measures within the community the rise in the rate of admissions will cease."

1. Report of the Ministry of Health for the year 1959, Part II. On the State of the Public Health: Being the Annual Report of the Chief Medical Officer. H.M. Stationery Office. Cmnd. 1207. Pp. 292. 13s.

In England Now

A Running Commentary by Peripatetic Correspondents

IT is possible to render a cat neurotic in the following way. First of all you teach it that food may be found under a certain lid. Then you teach it to step on a lever A to put the food there. Then you teach it that stepping on lever A only has this effect after a buzzer has sounded. Then you teach it to step on another lever B which causes the buzzer to sound. At this point the hungry cat, when put into the cage, goes to lever B, starts the buzzer, treads on lever A, sees the food travel along a moving belt to the box, and finally lifts the lid and takes the food. The mental state of the animal at this stage of its training might fairly be compared with that of a membership candidate, his brain the precarious repository of an elaborate, arbitrary structure of yeas and nays, do's and don'ts, almost amounting to the behavioural equivalent of a Calder mobile.

To return to the cat, it is instructive to watch the zest with which the experimenter next rigs up a cylinder of compressed air in such a way that, as often as not, but in no predictable sequence, the cat receives a violent air-blast in the face as it reaches triumphantly down into the box. After several of these rebuffs, the wretched animal grows disgusted with a world in which it receives only a silent Bronx cheer at the very moment when it expects, if anything, a spot of applause; it becomes apathetic, uncertain, withdrawn. It flinches at the sight of a mouse and has no heart for small talk with the fellers when it returns to the sane and levelheaded world of cats. It is, as you might say, a cool and far-out catnik. Several times a year one can see a silent, tight-lipped cortège of humans leaving Queen Square in this condition.

And now, the moral. The cat knows when it is beaten; whereas before it unerringly selected milk, now it totters on shaking paws to the dish of alcohol. But what of its human counterparts? These do not, let it be said, all take to drink; but with the regularity and persistence of the very seasons they return, time after time, to go through the same ritual and receive sooner or later the ineluctable blasting. This may not altogether go to show, as Clovis once put it, the superior wisdom of the cat tribe; but it makes you think, all the same.

* * *

It looks as though the West Country has lost its floods for the time being at any rate, though when the snow comes to the moors what will happen to the valleys is anyone's guess. But sufficient unto the day—down here we are busy scrubbing up for Christmas. The ground-floor rooms in those thousand flooded houses look much alike. Bare boards (for who would risk new lino or treasured carpet on still damp floors—a few rugs have to suffice), paper peeling from dripping walls, doors that will not shut, coldness and dampness everywhere. But the furniture, what there is left of it, is polished to perfection and the brass door-step is brighter than ever, and above all there are countless fires.

What of the inhabitants? There are some bruised shins and sprained ankles, the result of stepping into holes in the boards, a few colds, and fewer grumbles. What really does hurt is when other towns claim to have had bigger and better floods than ours. It just isn't fair! Anyhow we were one of the first on the news. Our houses were on the telly and we could even recognise our friends on the screen. We may salute Christmas with bare boards, bare walls, bare cupboards even, but salute it we will, and if the floods come again we will know how to deal with them and won't lose our carpets and lino the second time.

* * *

It had been a long unsatisfactory case, with an inevitable conclusion. The old man, on steroids for his chest, had failed to respond to medical treatment for his bleeding gastric ulcer. Postoperatively his abdomen had dehisced twice, and he had had a deep-vein thrombosis. His electrolytes had gone haywire, his serum-proteins had dropped, and he had become a pool of œdema. Then, finally, he had begun to bleed again.

The necropsy plodded on, nobody really learning very much. The physicians looked for a surgical "cause of death"; the surgeons were quite sure none of it would have happened if . . . So when the pathologist pulled a calcareous 5 cm. × 2·5 cm. solitaire out of the gallbladder and placed it with a bang on the table, everybody applauded the anæsthetist's soft comment: "Well, there is something concrete, anyway."

* * *

In my first house-job at the Z Royal Infirmary, I became convinced that the inhabitants of Z-shire had a bowel fixation. Whatever their complaint, from congestive cardiac failure to disseminated sclerosis, the patient's chief anxiety was centred on the presence or absence of constipation. Other symptoms and states might be unpleasant or inconvenient; only bowels were dangerous. The Medical Registrar, who had worked among the Zians much longer than I had, maintained that if you asked a Zian how his chest was, he would say "all right"; if you asked him how his stomach was, he would say "all right"; but if you asked him how his bowels were, he would say "all right, thank you".

* * *

It was a mild sunny Sunday morning, and the bustling animated crowd at Sandown Park might have been out for a carefree day at the races. But there were an unusual number of spectators in uniform—nurses, Civil Defence, ambulance, Red Cross, scouts, guides, and police. There were signs of strange mishaps, too, in the incongruously cheery casualties who strolled around, swathed in gory bandages, their faces ashen-grey with makeup and powder. In fact it was the Casualties' Union annual competition.

I had rashly offered to lend a hand supervising the National Blood Transfusion Service demonstration. My team was so expert that my own colour soon improved. A rubicund "donor" and a pallid "casualty" were laid out side by side on stretchers. "Blood" from drip-feed bottles ran to cannulæ in the antecubital fossa, artfully camouflaged with flesh-coloured plasticine. The inflow to the donor and the outflow from the casualty were concealed beneath the blankets. However, we all actually drank copious draughts of hot sweet tea, whenever the clot of spectators thinned.

The main event was the competition in which 24 ambulance teams from Service, police, Civil Defence, London Transport, and first-aid organisations had to diagnose three set casualties, render emergency first-aid, and get them into the ambulance within ten minutes. The "casualties" were strewn on the steps of the grandstand, acting the role of cleaners who had sustained injury while clearing up after the race-goers. It was interesting to watch how the teams went about it. I particularly relish the memory of a sweating policeman solemnly warning a casualty with a fractured tibia, "Now, you just stay where you are!"

* * *

The essential foreignness of a foreign country is never so strongly felt as in its hotels—the weird noises at odd hours, the cigar smells, the mysterious slept-in beds which appear overnight in the corridor, the pocket-filling keys attached to great bronze shields. But the things that really make me feel homesick and ill at ease are the notices. Sometimes this is because I cannot read them at all. "XPTHNTH TNY KRPTHNTHCXH!" declared an authoritative-looking plaque in an Athenian lavatory (Zeus! I remember wondering for a sickening moment—was I sitting in the right half of that bicameral establishment?) But usually it is their sheer threateningness that disconcerts me. "1. THE DIRECTION DON'T ANSWER FOR VALUES AND PRECIOUX THINGS, LEAVED UNGARDED IN THE ROOMS," growled a huge board in my Rome hotel. Aghast, I carefully locked my pitiful possessions in the wardrobe and pocketed another 4 in. key before going down to dinner. Next day, when the key jammed in the door, I struggled with it in a state of mad, unreasoning panic, fearful lest I be delayed and get involved in some terrible, foreign legal proceedings. For the next notice ran. "2. ROOMS DON'T DISAFFIRMED WITHIN 14 O'CLOCK ARE CONSIDERED CONFIRMED FOR THE NEXT DAY."

Letters to the Editor

REPRESENTATION OF REGIONAL BOARD HOSPITAL CONSULTANTS

SIR,—The council of the Regional Hospitals' Consultants and Specialists Association is concerned at the inadequate representation of consultants and specialists from regional-board hospitals on the various advisory and executive bodies which control the affairs of the National Health Service and of the medical profession. As a consequence of the National Health Service Act of 1948 consultants and specialists in regional-board hospitals number 85% of the total for England and Wales, and are responsible for over 90% of the clinical work in this country, but 53% of merit awards go to consultants in teaching hospitals.

	No. of beds	
Teaching hospitals	27,814	(6%)
Regional-board hospitals	455,818	(94%)

Our representation on the councils of the Royal Colleges is negligible, and Government committees set up to inquire into matters such as the staffing of our hospitals are often without anyone on them having had experience in running a large clinic in a regional-board hospital.

The National Health Service Act was negotiated without direct consultations with the consultants and specialists of non-teaching hospitals as a body, and now we have the "package deal" with its threat to part-time service. The abolition of "weighting" for new consultant appointments and of travel allowances will cost some consultants about £700 per annum to accept part-time contracts, and we wish as an Association to bring this and other anomalies to the attention of the Review Body at the first opportunity.

The method of appointment of senior registrars to consultant posts has given rise to widespread dissatisfaction caused by the preponderance of the teaching-hospital view, and this is especially so when, contrary to the wishes of the local hospital, a consultant is appointed who has been registrar to one of the teaching-hospital representatives on the advisory appointments committee.

Recently a questionnaire was sent to members and non-members of this Association. The replies received have been summarised as follows:

	Yes	*No*
(1) Are you satisfied that the present method of appointment of senior registrars and consultants is equitable:		
(*a*) with regard to the constitution of advisory appointments committees for		
(i) senior registrars	37%	45%
(ii) consultants	35%	52%
(*b*) as regards the merits of the candidates	51%	34%
(*c*) in that the majority of the consultants on the advisory appointments committee for non-teaching hospital appointments should be drawn from the teaching hospitals	14%	78%
(2) Do you consider that the present representation of consultants from regional-board hospitals is adequate on		
(*a*) the councils of the Royal Colleges	9%	81%
(*b*) the Joint Consultants' Committee	10%	76%
(*c*) other professional, regional hospital board, and Government committees	10%	77%

(In some cases those returning the questionnaire did not reply to all questions.)

We hope that consultants and specialists who are not members of the Regional Hospitals' Consultants and Specialists Association and who are in sympathy with the views expressed in this letter will communicate with the honorary secretaries.

V. COTTON CORNWALL
President
JOHN CAMPBELL
Honorary Secretary
H. A. KIDD
Honorary Secretary.

47, Lincoln's Inn Fields,
London, W.C.2.

DOES BUERGER'S DISEASE EXIST?

SIR,—Recent editorials [1 2] have thrown doubts upon the existence of Buerger's disease (thromboangiitis obliterans) and have suggested that it is merely an expression of atherosclerotic disease. This is a view that has a number of adherents and has been growing for some years. Whilst I would agree that certain of the criteria which have in the past been applied to this condition may be called in question, I think that a more critical examination is desirable before we accept such a conclusion.

One of the earliest critics of Buerger's conception was Fisher, [3] whose well-reasoned but cautious paper was largely based on five cases diagnosed as cerebral thromboangiitis obliterans, arising in elderly men who all had severe atherosclerosis. The affected small cerebral arteries had the appearance of "white strings", and this Fisher considered to be the result of bland thrombi forming on the distal side of atherosclerotic occlusions. The illustrations of these are beautiful examples of the canalisation of propagated clot, with normal veins. One is not disposed to quarrel with Fisher's interpretation, or with his conclusion that "cerebral thromboangiitis ... does not exist", but I doubt if it is legitimate to equate such lesions in non-anastomotic arteries with those of Buerger's disease in the limbs, and to argue for a similar pathogenesis.

Discussing the matter, Fisher refers to Lindbom,[4] making the point that in the latter's extensive study of arterial disease in the leg, thromboangiitis should have been observed, which was not the case. This does not necessarily follow, since Lindbom's examinations of the cadaver were made on a selection of elderly subjects all over the age of 50, the more elderly being preferred. Moreover, in the smaller arteries his pathological examination of the dorsalis pedis did not extend beyond the bases of the metatarsal bones, or of the posterior tibial artery beyond its division into the two plantars. He examined 80 of these cases histologically, and it is clear that his main preoccupation was with calcification. But in his clinical cases Lindbom refers to 7, all under the age of 40, in which no internal thickening was seen in such arteries as were patent. "In these cases the wall factor was, if existent at all, unknown."

Gore and Burrows,[5] who support Fisher, report 3 post-mortem examinations on males between 43 and 55, with extensive atherosclerotic disease and occlusive thrombi of small and medium arteries and occasional venous thrombi. They conclude that the "so-called pathognomonic appearance of thromboangiitis obliterans is precisely that of an organised and recanalized thrombus in a muscular artery without intimal or other disease". They seem, however, to imply the possibility of a distinct ætiology, since they quote my own observations [6] on the differences in the vascular pattern in Buerger's disease and atherosclerotic ischæmia. They add: "The basic lesion is arterial thrombosis which starts distally in small arteries and progresses by means of retrograde extension to the larger proximal channels." This is the converse of Fisher's explanation. "Evidence of primary arterial inflammation was not observed. Augmentation of the usual response to vasospastic stimuli is suggested as an explanation of the usual localization of the disease to the extremities." This conception is not really a denial of the existence of a Buerger syndrome, and it accepts a special ætiological factor provocative of thrombosis in the smaller vessels of the foot, with proximal progression, though in common with most recent writers the authors reject the inflammatory element which Buerger stressed.

The most recent paper is that of Wessler et al.,[7] who state

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that no cases of thromboangiitis have been diagnosed in their hospital in the past ten years, and on clinical grounds conclude that the disease does not exist as a separate entity. They also demonstrated, in the legs of cadavers subject to atherosclerosis, and in those amputated for atherosclerotic ischæmia, such changes as thrombosis, inflammation of the arterial wall, associated venous thrombosis and thrombophlebitis, perivascular and perineural fibrosis, &c., all of which have been claimed as evidence of Buerger's disease. In none was "any lesion resembling the acute specific histologic picture described by Buerger found in an artery or vein".

Such, in brief, is the gravamen of the case against Buerger's disease, and the arguments are sufficiently weighty to call for careful consideration. My own view is that the case is far from conclusive. I would agree that certain of the evidence put forward by Buerger (who I do not think from his writings was a very good histologist) is not wholly tenable: for example, his insistence on acute arterial lesions, "pyogenic foci", the alleged specificity of certain histological changes, and the significance of superficial venous lesions. But when all this is accepted there is, in my experience, a group of cases in young males in which the histological changes in the small peripheral vessels of the lower extremity mark them off from the commoner senile (or diabetic) gangrene due to atherosclerosis and thrombosis. Furthermore, these cases have clinical features on which my surgical colleagues diagnose them as thromboangiitis obliterans. The histological difference between these two classes of case is so clearcut that a differentiation can be made with a high degree of accuracy by simply examining sections of digits.

The points of difference are: in the Buerger group the lesions in the small vessels of the extremity are numerous and widespread, and involve both arteries and veins; the picture being one of thrombosis with active canalisation in vessels free from the degenerative changes of advanced life and progressive atheroma. These changes I have illustrated.[6] In atherosclerotic ischæmia, on the other hand, the smaller vessels of the extremity usually escape much damage; thrombosis in them is not common (apart from infective thrombosis in necrosing tissue), and venous alterations are the exception. It is difficult to explain these very real differences except in terms of a different process. If we are asked to assume that atherosclerosis of the proximal vessels is the cause of these peripheral changes, how is it that it produces this peculiar picture of arterial and venous thromboangiitis in the young and not equally in the elderly? It seems reasonable to expect a more efficient collateral circulation in the former and with it a diminished tendency to thrombosis. And yet this is the opposite of what we find. The variations in distribution and severity of senile atherosclerotic lesions in the lower limbs in the aged in both sexes are almost infinite, and yet this does not in my experience of itself produce the peculiar clinical, radiological,[8] and pathological picture which characterises thromboangiitis.

Whilst it may be accepted that the histological descriptions given by Buerger are not wholly accurate, this does not invalidate the whole conception. For this reason it may be as well to discard the eponymous title and to use the term thromboangiitis obliterans for this syndrome, which describes it accurately—at any rate in the lower extremity.

Research Department,
Mount Vernon Hospital,
Northwood, Middlesex.

J. HENRY DIBLE.

8. Steiner, R. *in* Peripheral Vascular Disorders (footnote 6).

SHINGLES AND CHICKENPOX

SIR,—Your annotation of Nov. 5 interests me as a general practitioner in a rural area which in many aspects is a "remote area". Chickenpox appears in undoubted epidemics, but shingles arises in crops or very small epidemics; and the relationship of chickenpox to shingles can usually be traced. This relationship is indirect, and I believe (without definite proof of course) that the changed infection is not transferred by direct contact, but that an intermediate host is necessary. In other words, the virus of chickenpox or shingles is carried by a healthy carrier, or perhaps more than one, and is manifest as a case of shingles or chickenpox.

This hypothesis is, of course, not invalidated by instances where both shingles and chickenpox arise in the same family; and it would explain the anomalies.

Petworth, Sussex. W. ANTONY BALL.

SUICIDE

SIR,—Dr. Casson's observations (Nov. 5) are of considerable medical and social importance, and require urgent and careful consideration.

The attitude to suicide adopted by the Church, and consequently by secular legislation, is not only inconsistent, but has sacrificed the greatest of Christian moral principles, charity, to fortuitous casuistry of very dubious ethical and social value. Although suicide is still regarded in this country, by both Church and State, as a crime (self-murder), there is nothing in the Old and New Testaments to justify such an attitude: while the earliest Patristic writings still allowed, or even approved of, suicide in certain cases, the Church unfortunately came to accept the uncompromising doctrine of Augustine (*De civitate Dei*, i, 16ff.), which interpreted the sixth commandment as including "self-murder" in whatever circumstances.[1 2 3]

With regard to the person who wishes, as Dr. Casson so well observes, "to terminate a life that has become a life-sentence of intractable pain", Thomas More maintained that priests and magistrates should in fact exhort him to put an end to a life which is only a burden to himself and to others. What I believe to be today the prevalent attitude towards suicide has been admirably stated by Westermarck[2]: "But common sense is neither a metaphysician nor a sophist. When not restrained by the yoke of a narrow theology, it is inclined in most cases to regard the self-murderer as a proper object of compassion rather than of condemnation, and in some instances as a hero."

The law as it stands includes the custom, mentioned by Dr. Casson, of presuming (whether for humanitarian or hypocritical reasons) that in such cases "the balance of mind was disturbed"—perjury, as Bentham said, being the penance which prevented an outrage on humanity. The rational and balanced arguments of such men as Thomas More, John Donne, Montaigne, Montesquieu, Voltaire, and Hume (to name but a few) cannot but shake the very foundations of this tenuous Augustinian doctrine of wholesale condemnation of "those sad souls", as Virgil called them, "who in innocence . . . flung away their lives".

In your report on a draft Suicide Bill (Oct. 29), you quote, as a (presumably enlightened) police procedure in cases of attempted suicide today, a statement that "A severe lecture or their stupidity is mostly delivered to the offenders by a seni officer", &c. Those who, through mental or physical illn intolerable pain and distress, or apparently insoluble emot or economic difficulties, are driven in desperation to at

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2. Westermarck, E. The Origin and Development of the M vol. 2, p. 229. London, 1908.
3. Westermarck, E. Christianity and Morals; pp. 250–59. I

Letters to the Editor

REPRESENTATION OF REGIONAL BOARD HOSPITAL CONSULTANTS

SIR,—The council of the Regional Hospitals' Consultants and Specialists Association is concerned at the inadequate representation of consultants and specialists from regional-board hospitals on the various advisory and executive bodies which control the affairs of the National Health Service and of the medical profession. As a consequence of the National Health Service Act of 1948 consultants and specialists in regional-board hospitals number 85% of the total for England and Wales, and are responsible for over 90% of the clinical work in this country, but 53% of merit awards go to consultants in teaching hospitals.

	No. of beds	
Teaching hospitals	27,814	(6%)
Regional-board hospitals	455,818	(94%)

Our representation on the councils of the Royal Colleges is negligible, and Government committees set up to inquire into matters such as the staffing of our hospitals are often without anyone on them having had experience in running a large clinic in a regional-board hospital.

The National Health Service Act was negotiated without direct consultations with the consultants and specialists of non-teaching hospitals as a body, and now we have the "package deal" with its threat to part-time service. The abolition of "weighting" for new consultant appointments and of travel allowances will cost some consultants about £700 per annum to accept part-time contracts, and we wish as an Association to bring this and other anomalies to the attention of the Review Body at the first opportunity.

The method of appointment of senior registrars to consultant posts has given rise to widespread dissatisfaction caused by the preponderance of the teaching-hospital view, and this is especially so when, contrary to the wishes of the local hospital, a consultant is appointed who has been registrar to one of the teaching-hospital representatives on the advisory appointments committee.

Recently a questionnaire was sent to members and non-members of this Association. The replies received have been summarised as follows:

	Yes	*No*
(1) Are you satisfied that the present method of appointment of senior registrars and consultants is equitable:		
(*a*) with regard to the constitution of advisory appointments committees for		
(i) senior registrars	37%	45%
(ii) consultants	35%	52%
(*b*) as regards the merits of the candidates	51%	34%
(*c*) in that the majority of the consultants on the advisory appointments committee for non-teaching hospital appointments should be drawn from the teaching hospitals	14%	78%
(2) Do you consider that the present representation of consultants from regional-board hospitals is adequate on		
(*a*) the councils of the Royal Colleges	9%	81%
(*b*) the Joint Consultants' Committee	10%	76%
(*c*) other professional, regional hospital board, and Government committees	10%	77%

(In some cases those returning the questionnaire did not reply to all questions.)

We hope that consultants and specialists who are not members of the Regional Hospitals' Consultants and Specialists Association and who are in sympathy with the views expressed in this letter will communicate with the honorary secretaries.

V. COTTON CORNWALL
President
JOHN CAMPBELL
Honorary Secretary
H. A. KIDD
Honorary Secretary.

47, Lincoln's Inn Fields,
London, W.C.2.

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One of the earliest critics of Buerger's conception was Fisher, [3] whose well-reasoned but cautious paper was largely based on five cases diagnosed as cerebral thromboangiitis obliterans, arising in elderly men who all had severe atherosclerosis. The affected small cerebral arteries had the appearance of "white strings", and this Fisher considered to be the result of bland thrombi forming on the distal side of atherosclerotic occlusions. The illustrations of these are beautiful examples of the canalisation of propagated clot, with normal veins. One is not disposed to quarrel with Fisher's interpretation, or with his conclusion that "cerebral thromboangiitis ... does not exist", but I doubt if it is legitimate to equate such lesions in non-anastomotic arteries with those of Buerger's disease in the limbs, and to argue for a similar pathogenesis.

Discussing the matter, Fisher refers to Lindbom,[4] making the point that in the latter's extensive study of arterial disease in the leg, thromboangiitis should have been observed, which was not the case. This does not necessarily follow, since Lindbom's examinations of the cadaver were made on a selection of elderly subjects all over the age of 50, the more elderly being preferred. Moreover, in the smaller arteries his pathological examination of the dorsalis pedis did not extend beyond the bases of the metatarsal bones, or of the posterior tibial artery beyond its division into the two plantars. He examined 80 of these cases histologically, and it is clear that his main preoccupation was with calcification. But in his clinical cases Lindbom refers to 7, all under the age of 40, in which no internal thickening was seen in such arteries as were patent. "In these cases the wall factor was, if existent at all, unknown."

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1. Rose, H. J. *in* Encyclopædia of Religion and Ethics, vol. 12, p. 21. Edinburgh, 1921.
2. Westermarck, E. The Origin and Development of the Moral Ideas; vol. 2, p. 229. London, 1908.
3. Westermarck, E. Christianity and Morals; pp. 250–59. London, 1939.

suicide, and pitifully have failed, are surely in need of the greatest possible assistance (inadequate as it may well be) of physical and psychological medicine, and expert social services: "a severe lecture on their stupidity" (*whose* stupidity?)—it may be supposed, to "bring them to their senses"—would seem not only superficial, pharisaic, presumptuous, and insulting to human intelligence and suffering, but as futile as the so-called remedies for the psychotic patient, to which Cælius Aurelianus (*On Chronic Diseases*, i, 5) referred somewhat ironically: "Some say he should be flogged, apparently so that he may regain his sanity by a kind of whipping of his reason." Our present laws on suicide are indeed reminiscent of the words of the judge, in Samuel Butler's *Erewhon*: "You may say that it is your misfortune to be criminal; I answer that it is your crime to be unfortunate."

The position on suicide adopted by the Church would appear to be morally and socially untenable, and, it may be hoped, will soon be legally unenforceable; from the medical and psychiatric point of view, it is absolutely inadmissible. Apart from being archaic in the light of contemporary medical and sociological advances, these ecclesiastical and secular laws and practices are based on bad theology: what, indeed, do they make (with their "unbalanced mind" mythology—if no longer requiring a burial at the crossroads) of those noble individuals who deliberately give their lives for their principles, their country, their family, and those whom they love? How, indeed, can their narrow and uncompromising attitude to suicide be reconciled with such high ethical concepts as these (*John*, x, 11; xv, 13): "the good shepherd giveth his life for the sheep"; "greater love hath no man than this, that a man lay down his life for his friends"?

Bransgore, Hampshire. R. H. AHRENFELDT.

STRONTIUM TURNOVER

SIR,—In the interesting article by Dr. Widdowson and her colleagues (Oct. 29) there is an error in relation to our strontium test of bone turnover in man.[1] We have used stable and not radioactive strontium, because we are not certain of the safety of introducing bone-seeking radioactive isotopes into the human body.

Postgraduate Medical School, London, W.12. RUSSELL FRASER MICHAEL HARRISON.

THE BORDERLINE FOR SEVERE SUBNORMALITY

SIR,—In their letter of Oct. 29, Dr. MacMahon and Dr. Clarke suggest that in the memorandum on parts I, IV–VII, and IX of the Mental Health Act, the Ministry of Health have taken the view that the borderline between subnormality and severe subnormality comes at I.Q. 70, or even rather higher.

As your correspondents point out, the Royal Commission on the Law relating to Mental Illness and Mental Deficiency considered that the test of severe subnormality should be the patient's inability to live an independent life; and they suggested that, using this criterion, it would very often be found that a patient with an intelligence quotient below the 50–60 level should be classified as severely subnormal. My understanding of the Mental Health Act is that the definitions of subnormality and severe subnormality in section IV are based directly upon the views expressed by the Royal Commission, and I cannot find anything in the Ministry's memorandum which in any way contradicts this view. As I read it, the passage referred to by Dr. MacMahon and Dr. Clarke merely indicates—as is surely the case—that many patients who will be classified as subnormal show both intellectual defectiveness and emotional instability. The fact that the words intellectually dull were used was not, I am sure, meant to imply that the division between the subnormal and the severely subnormal should be regarded as coming at some other point than that suggested by the Royal Commission.

Abinger Hammer, Dorking. W. REES THOMAS.

ORAL TREATMENT OF PERNICIOUS ANÆMIA WITH LOW DOSES OF H.P.P./1

SIR,—There is good reason to suppose that all the stores of vitamin B_{12} in the body are connected. This is supported by the finding of Ross and Mollin [1] that there is a similar organ distribution in normal and in deficient subjects, and also by various observations showing that in vitamin-B_{12} deficiency the B_{12} level is decreased to about the same extent in the various "subpools", such as liver, bone-marrow, and circulating blood.[2] This being so, a low vitamin-B_{12} serum level indicates a low total pool. If Dr. Mooney and Dr. Heathcote (Nov. 5) believe that their vitamin-B_{12}-peptide complex is absorbed better than ordinary crystalline vitamin, then in view of the subnormal or low serum-B_{12} levels one would be inclined to suggest that either it is quickly re-excreted in the urine or that an unusually large proportion of the vitamin is shifted to the tissues.

We suggest that Dr. Mooney and Dr. Heathcote carry out microbiological B_{12} serum assays on some of their patients treated with H.P.P./1, discontinue treatment, and establish the rate of decline of the B_{12} levels and also the interval before megaloblastic erythropoiesis recurs. Having done this, they may then conclude that with the doses they recommend they were unable to build up a satisfactory body pool of the vitamin. This will probably also give the answer to their insistence on having our explanation of the serum-B_{12} levels *on this particular form of therapy*. There is a difference between the minimum effective maintenance dose (0·5–1·0 μg. of vitamin B_{12} per day) and the dose required for the building up of a more than minimum body pool.

For our part we, like Dr. Shinton (Nov. 5), are satisfied that "as a general concept of rational therapy" 200 μg. or more daily would have to be given.

City General Hospital, Sheffield. S. VARADI A. ELWIS.

SIR,—After the interesting exchanges between Dr. Mooney and Dr. Heathcote and Dr. Varadi, might I venture to suggest that the argument is pointless?

Scientifically, it seems to have been established that the vitamin-B_{12}/peptide has destroyed the concept of Castle's intrinsic factor and changed our thinking in this respect; but the long-term oral treatment of pernicious anæmia by this compound must remain an unknown quantity irrespective of the serum-B_{12} levels.

I assume that patients maintained on this therapy have had it carefully explained to them that the treatment is new, the long-term effects unpredictable, and the prognosis consequently doubtful. Furthermore, that this treatment is being used instead of a proven method that can guarantee (in adequate dosage) no ill-effects from involvement of the central nervous system. Also, to ensure that subtle irreversible damage is not being produced either in the cerebrum or spinal cord, that these patients are being subjected to a complete neurological survey at least once a month. This survey must include examination of the visual fields and an electroencephalogram.

1. Fraser, R., Harrison, M., Ibbertson, K. *Quart. J. Med.* 1960, **29**, 85.

1. Ross, G. I. M., Mollin, D. L. Vitamin B_{12} in Tissues in Pernicious Anæmia and Other Conditions; p. 437. Stuttgart, 1957.
2. Gräsbeck, R. *Scand. J. clin. Lab. Invest.* 1959, **11**, 250.

Provided these standards are adhered to there seems only a very slight risk in maintaining patients on oral B_{12}/peptide. In my opinion, however, it is exceedingly doubtful whether there will ever be a place for this form of treatment in the alleviation of pernicious anæmia and/or subacute combined degeneration of the cord. Even if the patients preferred frequent pills to infrequent injections I am sure that most doctors would prefer to know that the vitamin B_{12} was firmly secured in two or three inches of muscle.

Institute of Clinical Research, Middlesex Hospital Medical School, London, W.1. A. D. M. SMITH.

NATURE OF ESSENTIAL HYPERTENSION

SIR,—We wish to comment on two of the statements made by Dr. Morrison and Professor Morris (Oct. 15) in relation to their study of London busmen.

(1) They state that "the drivers whose parent(s) died in middle age showed a bimodal distribution of blood-pressure". In fact, they showed a bimodal distribution of *systolic* blood-pressures only. Diastolic pressures were unimodal and, as we showed earlier,[1] their argument for hidden bimodality was based on a statistical artefact.

(2) They repeat their claim that there is more hypertension among the offspring of parents who die in middle-age than among the offspring of parents who die late, and this claim forms the basis of their whole study. In fact, as the following figures show, the mean pressures of the two groups of drivers are almost identical:

	Mean pressure of drivers Systolic	Diastolic
(*a*) Group with a parental death in middle age (n = 90)	153·7	89·7
(*b*) Group where both parents survived to old age (n = 96)	152·2	88·4

National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland. HARRY KEEN.

Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health, Baltimore. GEOFFREY ROSE.

DIAGNOSIS OF DIABETES

SIR,—Dr. Freeman (Oct. 29) is surprised at my finding [2] that 48% of a group of diabetics in Dundee had had continuous diabetic symptoms for more than four months and that 20% had noted these for at least a year before the diagnosis was made. He contrasts these findings with corresponding figures of 27% and 15% in his Exeter survey.[3]

I suggest that there is no need for surprise, because the 352 diabetics I studied and the 300 investigated by Dr. Freeman were dissimilar in a variety of ways.

His patients were restricted to those diagnosed in the years 1952 to (presumably) 1957 and attending one particular hospital, whereas mine are what I believe to be a representative cross-section of known diabetics in the Dundee area. In addition, my series differed in age at onset, and included a much higher proportion of females—particularly post-menopausal females. This latter group is, of course, especially prone to the slow insidious type of onset, which may partly account for the differences in our results.

It would, I agree, be unwise to suggest that my findings necessarily apply to all British diabetics and I have never claimed this. I can merely claim them to be typical of known diabetics in the Dundee area. Similarly, Dr. Freeman's own results can properly be applied only to a selected group of diabetics in a particular part of Devon. Even if he and I had used similar methods of sampling, the figures for Dundee and for Exeter need not necessarily be identical. The two populations may well be dissimilar in dietary habits. There may be differences between females in the areas both in reproductive histories and in anthropometric characteristics. For these and other reasons the epidemiological patterns of diabetes in Dundee and in Exeter might differ and this could have an effect on the type of onset.

The other matters raised by Dr. Freeman are interesting, as was his original paper on the subject. I should like to comment on his figures in the light of my own findings but, once again, comparison may be misleading because of different methods of selection and classification. I hope in due course to publish the full results of my studies, with details of the criteria used.

Meanwhile, may I emphasise the deficiencies in our knowledge of the true epidemiology of diabetes mellitus throughout Britain. Most reports dealing with the subject refer only to known diabetics and, in particular, to those on the books of hospital diabetic clinics. There are signs that professional and public interest in the early detection of the disease is now increasing. Until there is general agreement on the importance of searching for hitherto undiagnosed diabetics, instead of waiting until they present themselves after months or years of symptoms, our epidemiological knowledge will remain inadequate.

I found Dr. Freeman's statement that 15% of his diabetics had had symptoms for a year or more before being diagnosed to be little more reassuring than my finding of 20%. If either figure were applicable to the country as a whole, it would represent a vast amount of needless human suffering. For that reason, I welcome your leading article (Oct. 1) as yet another reminder of the importance of adopting a more vigorous policy towards diabetes detection.

Ravensthorpe, Northants. J. J. A. REID.

1. *Lancet*, 1959, ii, 1028.
2. Reid, J. J. A. *Med. Offr*, 1960, **103**, 325.
3. Freeman, A. G. *Brit. med. J.* 1958, i, 1149.

BROADER MEDICAL TEACHING

SIR,—I should like to support every word of Dr. Cardew's letter of Nov. 5. As a consultant, who started as a G.P.-surgeon, I can speak from some personal experience. My basic training in general practice has been more than useful.

The man entering general practice has received no teaching on the treatment of the minor ills of this life. As such conditions constitute the bulk of his practice, any ideas on treatment from the advertisers are of course gratefully received. Unfortunately the mere prescription of some new drug or form of support is but a minor part—if a part at all—in the treatment of many of these conditions. I have discussed this at some length in a treatise on my own specialty in general practice.[1]

Many in the profession (consultants included) are now content to be mere tradesmen recommending advertised goods. Only by a better training can we set our house in order and maintain a true professional standard.

Tunbridge Wells. W. H. GERVIS.

SIR,—The medical student does not expect the gynæcologists to teach him about eyes; nor does he expect hospital consultants and registrars to instruct him in general practice. It is by attending patients with a good family doctor that the would-be general practitioner can learn his work quickly. Experience gained at first hand by a G.P. trainee must far outweigh vicarious experience handed out by a hospital specialist who has, perhaps against his better judgment, spent six months in compulsory general practice.

Dr. Cardew suggested (Nov. 5) that every future teacher in the hospital service should, between the appointments of registrar and senior registrar, spend four consecutive periods of six weeks attached to each of four different types of general practice (industrial, semi-urban, rural, and seaside). I fail to see how this would effectively broaden medical teaching, or who could gain from such a plan.

1. Orthopædics in General Practice: Is It Rheumatism, Doctor? London, 1958.

The limited time spent in each type of practice would not give anyone the opportunity of appreciating for himself that especial satisfaction found in giving medical care to the same people over a period of years, or even over several decades.

The only registrars enjoying the experience would be those least in need of that experience—those who already have wide interests, including an understanding of their fellow men. The registrars who would consider the half-year in general practice as time wasted, perhaps because they are already engaged in some research project in their own specialty, could gain little other than a feeling of frustration.

The patient could derive no benefit from the plan, for he likes to consult the practitioner whom he knows and who knows him. If, on the other hand, the future hospital teacher is present only as an observer, who would pay his salary?

London, S.E.4. MARY RESTELL.

HEALTH OF EXECUTIVES

SIR,—Our Health Conference for Business Executives fixed for Nov. 24 in the Royal Festival Hall is arousing considerable interest. Some doctors are asking "But why business executives? Do we not all need health education?"

The triumphs of preventive medicine are chiefly in childhood and youth. It has still to make its impression on the afflictions of middle-age. Men and women who bear stress and responsibility need health education badly, and not only from the personal point of view. Their decisions can influence the health and fitness of large numbers of employees.

This is the main reason for the conference, which merely continues what the Chest and Heart Association has been doing for sixty years. We have always encouraged the participation of laymen in our meetings, and this policy has been well worth while.

This year, President Eisenhower's physician, Dr. Paul Dudley White, pays us the compliment of coming over specially to speak on coronary thrombosis.

HARLEY WILLIAMS
London, W.C.1. Secretary-General, Chest and Heart Association.

BINDING BOOKS

SIR,—Your review (Nov. 5) of *Lectures on Hæmatology*, edited by F. J. G. Hayhoe, suggests that this book and others in the same series might well be published "in a less expensive form—say, paperback with plastic binding and without some of the illustrations". The point about the illustrations is being considered by our editorial office; but the rest of the suggestion is based on a persistent fallacy which bedevils all discussions about book prices and really ought now to be discarded.

To bind a book in paper instead of in a hard binding produces a quite insignificant economy. In paper the *Lectures on Hæmatology* might be retailed at 58*s.* 6*d.* instead of 60*s.*, its price in hard covers. (The use of the thermoplastic process instead of stitching is only possible if a minimum of 5000 copies are bound at one time, and even this would not save more than another shilling.) The thing, and the only thing, that makes a paperback (in the modern sense) cheap is that it is printed in enormous quantities at a time. The readers of a technical work, such as the *Lectures on Hæmatology*, must be strictly limited however cheap its price.

R. W. DAVID
Manager,
London, N.W.1. Cambridge University Press.

PROGNOSIS AND PROPHYLAXIS AFTER CORONARY OCCLUSION

SIR,—Professor McMichael and Dr. Parry's magnificent summary (Nov. 5) of the case against anticoagulants will no doubt stimulate a number of powerful counterblasts. This does seem to be a subject which has produced as much statistical prestidigitation and high feeling as any—probably because of the absence of any other prophylactic treatment for the disease, the difficulties and dangers of the treatment, and maybe because of disappointed expectations of the results of treatment. It is natural to seize on this only hope of doing something to prevent recurrence of such a dread disease. In addition, anybody who has experience of the treatment will know how quickly patients come to believe that it is lifesaving—a belief which the doctor often fosters, both to justify the dangers involved, and also to induce the necessary discipline which will reduce these dangers and make the treatment better "controlled". One overstates the case, and then desperately hopes the overstatement will be proved to be right. On the other hand, if the patient is not given the treatment there is a sneaking feeling that he may be being denied his only chance. It is hard to imagine a more guilt-producing situation!

It seems to me that too much has been expected of anticoagulants in the treatment of ischæmic heart-disease and the prophylaxis of myocardial infarction. In this disease atherosclerosis causes progressive narrowing of the coronary arteries with or without thrombosis in them. As the narrowing proceeds collateral vessels develop. These processes cause gradual myocardial degeneration punctuated by acute episodes of myocardial infarction. These episodes are usually the result of coronary thrombosis, but may not be. The relative importance of these various factors in the disease will vary from patient to patient. In young patients atherosclerosis will be less far advanced, and thrombosis will be relatively more important. In older, diabetic, hypertensive, and fat patients atherosclerosis may be expected to be the more important factor. Similarly, patients who have evidence of widespread myocardial disease such as heart-failure, hypotension, arrhythmias, enlarged heart, and recurrent infarction (the so-called bad-risk cases) are those who may be expected to have widespread coronary atherosclerosis. (Bjerkelund's [1] cases with a "high force of recurrence" presumably come into this group.)

Parallel with this varying pathological picture it is found clinically [2] that young patients are more likely to have serious infarcts (presumably because collaterals have not had time to develop), but if they make an uncomplicated recovery they have a good prognosis (because their myocardium is healthy), and are more likely to die of a further infarction. Conversely older and bad-risk patients have less serious infarcts (because collaterals have had time to develop), but are more likely to die of myocardial failure, and have a worse prognosis.

Anticoagulants are likely to be most effective in preventing coronary thrombosis, and to have little or no effect on progress of atherosclerosis. Prophylaxis may be expected therefore to be most effective in those patients in whom thrombosis plays the greater part—i.e., in young good-risk cases. This is what has been found in both Bjerkelund's [1] and the Medical Research Council [3] trials. Thus, the M.R.C. reported a fivefold reduction in recurrent infarction in their treated group, and the improvement lasted for at least two years. In spite of this the reduction in mortality was only about one half, and that only during the first six months of treatment. This is most mysterious because reinfarction is much the commonest cause of death in this age-group. In Honey and Truelove's young patients the incidence was 75%. The answer may lie in the vexed question of the diagnosis of reinfarction. There may

1. Bjerkelund, C. J. *Acta med. scand.* 1957, **158**, suppl. 330.
2. Honey, G. E., Truelove, S. C. *Lancet*, 1957, i, 1209.
3. *Brit. med. J.* 1959, i, 83.

have been unwillingness to diagnose reinfarction in the treated group unless the patient actually died: this would have the effect of increasing the apparent mortality of, and the apparent reduction of, reinfarction. Bjerkelund's figures show a much closer correlation between reduction of reinfarction and mortality in his treated group of young patients, the incidence being two-fifths and four-sevenths respectively. He was more definite about his diagnosis of reinfarction and also had a much more complete postmortem follow-up. His postmortem studies did show that the incidence of coronary thrombosis in patients who died of recurrent infarction was halved by anticoagulant treatment.

Thus, both these series do show a certain reduction in the reinfarction-rate. Bjerkelund's postmortem studies do provide direct evidence that anticoagulants can reduce the incidence of coronary thrombosis as the cause of the reinfarction. On the other hand, the absence of a reduction in mortality after at the most a year shows that there is inexorable progression of the atherosclerosis, in spite of treatment. More and more patients must go on to the stage of widespread arterial disease and myocardial degeneration, in which anticoagulants cannot be expected to be so helpful, and die of heart-failure; or they may die a sudden death (sudden death without infarction is commonest in sclerosis alone [4]). In addition to the reduction in coronary thrombosis Bjerkelund did find a reduction in mural thrombosis in his treated patients at postmortem. Although Gilchrist and Tulloch [5] found little difference in mural thrombosis, there was a reduction in systemic emboli in their series.

I believe that there is a case for long-term prophylactic treatment of coronary-artery disease with anticoagulants. It is not possible to say for certain in the individual patient what relative parts thrombosis and sclerosis have played and will play in the development of the disease, although likelihoods can be assessed on the grounds described above. The greater the part thrombosis plays, the more valuable is treatment likely to be. Patients should be reviewed every six months, and any who are developing signs of widespread myocardial disease can be rejected, particularly those whose treatment is difficult to control. Those with no such signs can be continued on treatment. Possibly unconscious selection along these lines is what has produced such favourable results in some series. Patients who present with angina or acute coronary insufficiency should be treated in the same way. Postmortem evidence shows that both these symptoms may be associated with coronary thrombosis, and indeed the good effect of anticoagulants in acute coronary insufficiency in preventing definite infarction [6] is further indirect evidence that they can prevent the spread of coronary thrombosis. The prognosis of patients presenting with angina is the same as those presenting with infarcts,[7] and logically they should be assessed for treatment in the same way.

There is a tendency for all-or-none opinions to be held about this treatment. Perhaps the best course is careful selection of patients for treatment, the length of which should be suited to the individual patient. If patients are not led to believe that treatment is lifesaving, stopping it will be easier.

University College Hospital,
London, W.C.1. P. M. S. GILLAM.

SIR,—The paper by Professor McMichael and Dr. Parry (Nov. 5) is refreshing to those, like myself, who think that the case for long-term and possibly even immediate treatment with anti-prothrombin agents in coronary thrombosis is not yet proven.

The paper should help to prevent abuse of such therapy. At present, some physicians give it in virtually all cases of coronary thrombosis and angina of effort on a long-term basis: not to do so, they feel, may be to the detriment of their patients. Anticoagulant clinics have sprung up in many hospitals, dealing with hundreds and sometimes with a thousand or more cases, and I have heard of a pathologist who spent a considerable part of his day in the estimation and advice on these tests. What is really required is follow-up—whenever possible, of large series over ten years or more—of cases treated with or without anti-prothrombin agents.

A surgeon who has carried out major surgery on patients receiving anti-prothrombin agents assures me that there was no abnormal tendency to hæmorrhage in these cases. This is difficult to understand in view of the alleged value of such drugs in preventing clotting; yet it need not be so surprising, since it is recognised that the clotting-time in patients on anti-prothrombin agents, despite prolonged prothrombin-time, may be quite normal. There need not therefore be any correlation between prothrombin-time and clotting-time. The position may be different with heparin, which prolongs the clotting-time; but at present no oral heparin or heparinoids are available, and long-continued therapy with these drugs is therefore not feasible.

It seems to me that we should adopt a more guarded attitude, and not allow ourselves to believe that we should be failing in our duty to our patients if we did not use anti-prothrombin agents in every case of angina pectoris and coronary thrombosis.

St. Mary Abbot's Hospital,
London, W.8. B. GOTTLIEB.

ETHIONAMIDE

SIR,—Your leading article of Oct. 29 mentioned the trials which are being carried out by the research committee of the British Tuberculosis Association in which this drug is used for the treatment of patients with advanced pulmonary tuberculosis in whom previous treatment with streptomycin, isoniazid, and P.A.S. has failed. You stated in error that in these trials a group of patients is being treated with ethionamide and cycloserine; in fact, this combination is not being used.

The reasons for not using this combination were provided by the results of a preliminary trial reported by Riddell, Stewart, and Somner [1] in which patients were given ethionamide 0·5 g. daily with either cycloserine 0·5–1 g. daily or pyrazinamide 2–3 g. daily (according to body-weight). This dose of cycloserine appeared inadequate to protect completely against the emergence of cultures with decreased sensitivity to ethionamide. Increase in the dose of cycloserine was not thought to be practicable because of its side-effects, so that the combination of cycloserine with ethionamide alone is not used in the present trial.

On the other hand, in the preliminary trial [1] the dose of ethionamide (0·5 g.) appeared insufficient completely to prevent decrease of pyrazinamide sensitivity. In view of this in the present trial the recommended dose of ethionamide has been increased to 1 g. daily in combination with pyrazinamide. A second group of patients is being treated with ethionamide (1 g. daily) with pyrazinamide and cycloserine, to see if this combination will prevent the emergence of resistance to these drugs. Patients are being allocated at random to these two treatment groups (i.e., either ethionamide plus pyrazinamide, or ethionamide plus pyrazinamide and cycloserine). In addition a separate trial is in progress to study treatment with ethionamide and streptomycin in patients whose organisms are thought to be resistant to isoniazid and P.A.S.

The British Tuberculosis Association Research Com-

4. Yater, W. M., et. al. *Amer. Heart J.* 1948, **36**, 334, 481, 683.
5. Gilchrist, A. R., Tulloch, J. A. *Scot. med. J.* 1956, **1**, 1.
6. Wood, P. Diseases of the Heart and Circulation. London, 1956.
7. Seims, E. *Acta med. scand.* 1960, **166**, 255.

1. Riddell, R. W., Stewart, S. M., Somner, A. R. *Brit. med. J.* 1960, ii, 1207.

mittee share the hope expressed in your article that these controlled cooperative investigations will eventually provide much information of value for treating those in whom initial treatment has failed. Should your readers in Great Britain have patients they would like included in the trial, I would be pleased to send them a protocol.

K. M. CITRON
Institute of Diseases of the Chest, Brompton, London, S.W.3. Coordinator, British Tuberculosis Association Ethionamide Trial.

*** We are grateful to Dr. Citron for correcting our mistake.—ED. L.

SPORTS MEDICINE

SIR,—I was much interested in Dr. Troup's paper of Sept. 24. What most surprises a Continental medical observer is that this specialty, widely accepted and practised in so many countries (may I add Italy and France to Dr. Troup's list?), has been relatively unknown in your country and in the United States, which in many ways are leading countries in the development of sport.

To the many positive aspects of sports medicine mentioned in Dr. Troup's paper I would add some observations. The athletic performances of recent years, pushed to the limits of human endeavour, represent a form of experimental research which physiopathologists should not miss. The true meaning of some structural or functional changes induced by exercise has still to be determined. There also remains the problem whether these indicate a pathological state or are an expression of a specific physiological condition. In this respect, much is known about the cardiorespiratory mechanism of adaptation to physical stress, but little information is available on the behaviour, for instance, of the endocrine system and of the antitoxic functions.

We hope that the work of the Fédération Internationale Médecine Sportive can attract the attention of doctors and research-workers and stimulate them to take part in the development of this new branch of medical science.

GIUSEPPE LA CAVA
Via Antonio Serra, 104, Rome. Secretary-General, Fédération Internationale Médecine Sportive.

A NEW TYPE OF CHROMOSOMAL ABNORMALITY IN GONADAL DYSGENESIS

SIR,—We have studied the somatic chromosome complement of three female patients having primary amenorrhœa, infantilism, short neck, and undeveloped secondary sexual characteristics. They had elevated levels of urinary gonadotrophins and low levels of urinary œstrogens. Laparotomy in two of them revealed an undeveloped uterus and "streaks" of rudimentary tissue at the site of the gonads. The three patients were sex-chromatin positive and their bone-marrow and skin cells cultured in vitro yielded counts of 46 chromosomes.

Two of the patients were independently selected, in two different clinics, as Turner's syndrome, one in March, 1959, and the other in January, 1960. The third one was selected under the influence of the findings of the other two because she was a sex-chromatin positive, "atypical" Turner.

Detailed study of the karyotypes revealed in all of them the presence of only one X chromosome and of a long, metacentric, chromosome which, on morphological evidence, was similar to the chromosomes of pair no. 3.

The most likely interpretation of these karyotypes is that the abnormal chromosome is an "iso-chromosome" for the long arm of one X chromosome. The patients are therefore formally trisomic for the long arms and monosomic for the short arm of X, but two of the long arms must be, by the definition of iso-chromosomes,[1] genetically homologous. Other possible interpretations include duplication of part of one of the X chromosomes, translocation of other chromosomal material on to one X chromosome, and trisomy for chromosome no. 3 and monosomy for the X chromosome.

While we are preparing a detailed description of these cases, we wish to call attention to the fact that analysis of the karyotype may reveal peculiar cytological situations which are relevant to a better understanding of gonadal dysgenesis as shown by the case reported by Jacobs et al.,[2] and by those mentioned here.

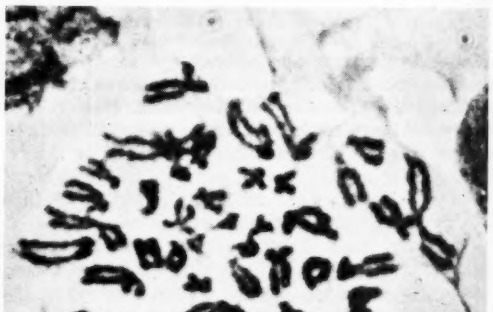
Medical Research Council, Population Genetics Research Unit, Old Road, Headington, Oxford. M. FRACCARO.
Department of Endocrinology, Karolinska Hospital, Stockholm. D. IKKOS, J. LINDSTEN, R. LUFT.
Department of Pædiatrics, Central Hospital, Eskilstuna, Sweden. K. KAIJSER.

CHROMOSOMES IN HYDATIDIFORM MOLES

SIR,—In 1940 Hertig and Edmonds, in their treatise[3] on the genesis of hydatidiform mole, said that "the disappearance, degeneration or even necrosis of the vascular 'anlagen' (in the chorionic villi) is nothing but a variety of disuse atrophy and does not represent a primary abnormality of the chorionic vessels". Edmonds[4] pointed out that hydatidiform mole "could be induced by the combined action of a chromosomal factor present in the ovum and a maternal constitutional or age influence".

Support for the presence of a chromosomal factor in the villi has been found by counting chromosomes in the villi of hydatidiform mole.

In three cases mole tissue, as fresh as possible, was put into distilled water, transferred to 45% acetic acid, squashed, hydrolysed, and stained with Feulgen reagent or Klinger reagent.



Sex-chromatin positive hydatidiform mole. "Plate" showing squashed metaphase, 38 chromosomes. Slightly different focus and photography allow accurate charting of chromosomes. (Feulgen. × 3200.)

In the first mole, in 2 cells 46 chromosomes, and in 9 cells 38 chromosomes were counted. In the second mole, only 1 cell was so well preserved that chromosome counting was feasible: the number was 38. In the third mole, in 7 cells 38 chromosomes were counted (see figure), in 2 cells 39 chromosomes, in 9 cells 46 chromosomes, and in 1 cell 47 chromosomes. Karyotyping of the 38 chromosomes proved to be extremely cumbersome and is still under study.

So, in our opinion, the lack of vessels in the chorionic

1. Darlington, C. D. *J. Genet.* 1940, **39**, 351.
2. Jacobs, P. A., Harnden, D. G., Court Brown, W. M., Goldstein, J., Close, H. G., MacGregor, T. N., Maclean, N., Strong, J. A. *Lancet*, 1960, i, 1213.
3. Hertig, A. T., Edmonds, H. W. *Arch. Path*, 1940, **30**, 260.
4. Edmonds, H. W. *Ann. N.Y. Acad. Sci.* 1959, **80**, 86.

villi of hydatidiform mole may be regarded as a primary defect in the formation of the villi in this disease and not as a disappearance of the vascular anlagen, caused by "the early death of the fœtus". According to this view hydatidiform-mole villi could be regarded as persistent secondary villi (whereas in chorio-epithelioma the process of formation of the villi is probably arrested in the primary stage).

L. A. M. STOLTE
H. I. A M. v. KESSEL
J. C. SEELEN
G. A. J. TIJDINK.

University Department of Obstetrics and Gynæcology, St. Radboudziekenhuis, Nijmegen, Netherlands.

ARTIFICIAL INSEMINATION

SIR,—Concerning the astonishing suggestion that A.I.D. constitutes adultery even if performed with the full consent of the husband, and its defence that it is not sinful since concupiscence is lacking, I should propose to make *intent* the crucial test for marital deception.

Having a child through A.I.D. is analogous with adopting a baby, and *not* with bearing a child conceived in adultery. A.I.D., like adoption, is dependent upon the consent of both husband and wife; it is an open act performed for a socially accepted purpose, and it lacks the intent to deceive. Making a concession to human nature, it appears good practice to mix the semen of the donor with that of the husband before performing A.I.D. The uncertainty introduced seems to help avoid an emotional stress on the husband; it is not the element of adultery, but the closer physical ties between child and mother that carry the seeds of conflict. In this way *pater semper incertus est* remains true.

San Francisco. STEVEN E. ROSS.

SIR,—Dr. Audrey Roberts (Oct. 29) need not take so gloomy a view of moral theology. It can, and does, move with the times. No longer, for example, do its interpreters think it seemly to burn heretics at the stake: a distinct advance.

Crediton, Devon. L. N. JACKSON.

RESPIRATORY OBSTRUCTION DUE TO FAULTY ENDOTRACHEAL TUBE

SIR,—I should like to suggest that this phenomenon is more often due to the use of too small an endotracheal tube than to a fault in the tube.

In one case reported a no. 6 or 7 tube was used for an adult patient; to obtain an airtight seal in an adult trachea with a tube of this size inevitably leads to an overdistension of the balloon with consequent bulging of any weak part in the balloon.

In order to provide the patient with the best possible airway it is important to select the largest bore endotracheal tube that can be passed through the glottis without trauma; in my experience there is rarely a need to use anything smaller than a no. 10 in an adult and I very frequently use a no. 11 or 12. With tubes of these sizes an airtight seal within the trachea can be obtained with a minimum of distension of the balloon and consequently a minimum risk of causing the balloon to herniate or burst, with the possibility of obstruction in the one case and damage to the trachea in the other.

Two points in the care of endotracheal tubes are of importance: always place the balloon end of the tube in a test-tube when testing the tube by inflation (this prevents overdistension of the balloon and a weakening of its wall during the test); and avoid the use of tube lubricants which have a fatty base (such lubricants have a very deleterious effect on the thin rubber of the balloon and weaken the wall, thus predisposing to bulging under inflation).

Ferndown, Dorset. S. F. DURRANS.

DRIVING AND CORONARY THROMBOSIS

SIR,—During the past fourteen months I have seen 10 cases of coronary thrombosis, in 8 of which the patients had been driving their car in London just before the attack. 3 of the patients drove themselves to my consulting-room and their attacks occurred during the journey. The other 5 had attacks on arriving home after driving in London (1 patient collapsed after garaging his car).

The traffic in London becomes more and more congested every day and the stress of driving is proportionately increased. I am sure this stress and accompanying exhaustion, especially during the peak hours in London, is a cause of many coronary thromboses. But exhaust fumes may contain vasoconstrictor substances that act as a substantial contributory factor. In view of present-day conditions, I do not support the suggestion that driving can be a form of relaxation.

London, W.1. MAX ODENS.

POMP AND CIRCUMSTANCE

SIR,—What! Abolish teaching ward rounds? No, Never. It's the one bright spot in the patient's week, to hear the students and doctors cross-questioned. At least, so I have been told by many ex-ward-patients.

London, W.1. G. E. BEAUMONT.

DANGERS OF ORAL DIURETICS IN A HOT CLIMATE

SIR,—The use of diuretics such as chlorothiazide and hydrochlorothiazide as hypotensive drugs for non-œdematous patients has lately increased considerably. The following case illustrates how these drugs may produce severe hypotension if not adequately controlled.

A woman of 69, who had never shown signs of cardiac failure, was treated in the U.S.A. with hydrochlorothiazide for more than 2 years. Her blood-pressure before treatment was about 220/100 mm. Hg and was controlled by 25 mg. of hydrochlorothiozide twice daily at around 160 systolic and 80–90 diastolic. She kept to this regimen when she arrived in Israel for a visit. After her arrival she had diarrhœa for several days. Subsequently, on a very hot day, when the dry eastern winds (khamseen) prevailed she took a trip by bus (10–11 hours from Haifa) to Elath on the shore of the Red Sea. The temperature there was 42°C (107·6°F) with relative humidity below 10%. As she had not felt well on the previous days she had increased her dose to 75 mg. daily without consulting a doctor. At Elath she felt, as she said, extremely weak and could hardly move. Next morning she went back by plane and arrived with great difficulty at her temporary residence near here. She rested and called me, for the first time, on the fourth day after her return. Her blood-pressure was 95/45. As she had stopped taking the drug 3 days previously it can be presumed that her blood-pressure was lower still at Elath and that she had been in a state of near collapse. An electrocardiogram next day showed no myocardial damage and no signs of potassium depletion, but evidence of left heart strain. As she refused further examinations, no estimation of electrolytes or plasma-volume was made.

Recovery was quick and uneventful. Without any medication her blood-pressure returned to 150/80 within 16 days and remained so till her departure from Haifa.

This case showed a combination of several factors: dehydration after diarrhœa and exposure to a hot dry climate without sufficient intake of fluid, aggravated by an increased dose of hydrochlorothiazide, combining to induce dangerous hypotension.

Similar reactions, though not as dramatic, were seen lately in two other patients, also new arrivals from abroad and not yet

acclimatised, who kept to their former doses of hydrochlorothiazide.

For many years it has been known in this country—before the start of oral diuretic treatment—that regular mersalyl injections had to be stopped when the khamseen blows (a hypotensive agent in itself). Doctors who know that patients on hypotensive drugs intend going abroad should warn them to be careful in an unfamiliar climate.

Haifa, Israel. H. W. BRUNO.

TREATMENT OF FANCONI'S ANÆMIA

SIR,—Interest in the treatment of this condition has been reawakened by a report [1] of the use of a combination of testosterone and prednisone in aplastic anæmia in children. The bone-marrow regenerated in 4 out of 5 cases so treated, and 1 of these was a Fanconi's anæmia. Later figures indicated moderate to full remission in 11 out of 17 cases on this treatment: 3 showed no response and 3 died in the early stages of treatment.[2]

It was decided to try this treatment in Cape Town in a brother and sister with Fanconi's anæmia. The disease and its occurrence in 5 children seen here has been described elsewhere.[3] 3 of the 5 patients were members of one family, which included the 2 children and an elder sister who died of the disease in 1957.

CASE 1.—A boy, aged 7 years, was first seen by us in 1959 and was found to have Fanconi's anæmia. The anæmia was not severe, but he had associated thrombocytopenia and neutropenia with a hypocellular marrow and several congenital defects. Treatment with methyl testosterone (25 mg. daily) and prednisone (10 mg. daily) began in January, 1960. After 3 months his hæmoglobin, though not showing a spectacular rise, was nevertheless maintained without transfusion during this time. He had previously had two transfusions over a period of 5 months (fig. 1). He also had a platelet and a neutrophil response. The platelets, which had varied between 50,000 and 70,000 per c.mm., had risen to over 100,000 and his neutrophils from between 2% and 34% to 66%. The previously hypocellular marrow showed considerable activity, particularly of red-cell precursors.

CASE 2.—A girl, 11 years old, first came to us a few months before her brother and the initial diagnosis was aplastic anæmia. When the brother was seen and his congenital defects observed, the girl was re-examined and found to have deficient thenar muscles on one hand as well as some pigmentation which had not previously been appreciated. Her peripheral blood showed essentially the same features as the boy, but to a greater degree. She had several marrow aspirations and one trephine of the iliac crest, and all showed very defective marrow activity. She required four transfusions at intervals of approximately 2 months.

Treatment also began in January, 1960—prednisone (10 mg. per day) and methyl testosterone (50 mg. per day, 2 mg. per kg. per day in each child). 3 months later (April 1, 1960) her hæmoglobin had risen from 9·8 g. to 13·1 g. per 100 ml. and she had needed no transfusions during this time (fig. 2). Her bone-marrow also showed erythropoietic activity and both platelets and neutrophils were rising from their previously low levels.

In Shahidi and Diamond's patients the first response was always in the red-cell series and the other blood elements showed signs of regeneration later. It was usually 2–3 months before benefit was seen, so that in our cases we may find a further increase in platelets and neutrophils later.

1. Shahidi, N. T., Diamond, L. K. *A.M.A.J. Dis. Child.* 1959, **98**, 293.
2. Diamond, L. K. Personal communication, 1959.
3. McDonald, R., Goldschmidt, B. L. *Arch. Dis. Childh.* (in the press).

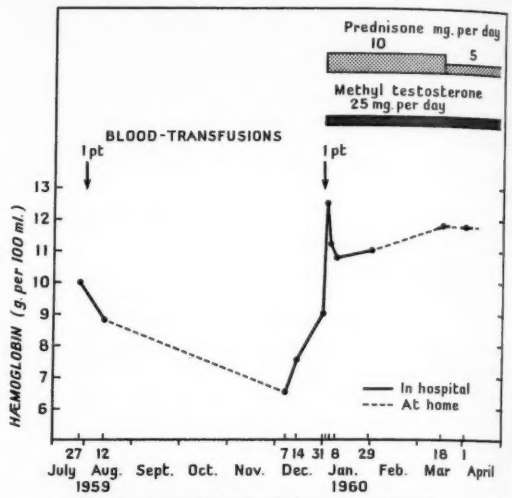


Fig. 1—Hæmoglobin levels in case 1, a boy of 7.

Side-effects in both children so far have been slight acne, some flushing, and "Cushing" appearance; and both have developed pubic hair. In addition, the boy has shown some enlargement of the external genitals. They both feel very well, have large appetites, and are no longer easily fatigued.

Because of the Cushing effects the dose of prednisone has been reduced to 5 mg. daily in each case and there has been some decrease in the children's weights. In view of the genital overgrowth in the boy, it may be desirable to reduce the dose of methyl testosterone, but for the present it is being kept at the starting level.

The results, especially in the girl, seem promising, but more than this cannot yet be claimed. According to Shahidi and Diamond,[1] therapy will have to be continued for at least another 6 months, and it remains to be seen whether the improvement will thereafter be maintained without treatment. It is not yet known whether further courses of the drugs are necessary or not. This will depend on follow-up studies of peripheral blood and bone-marrow.

The future may show that complete recovery is sometimes possible from this hitherto fatal disease.

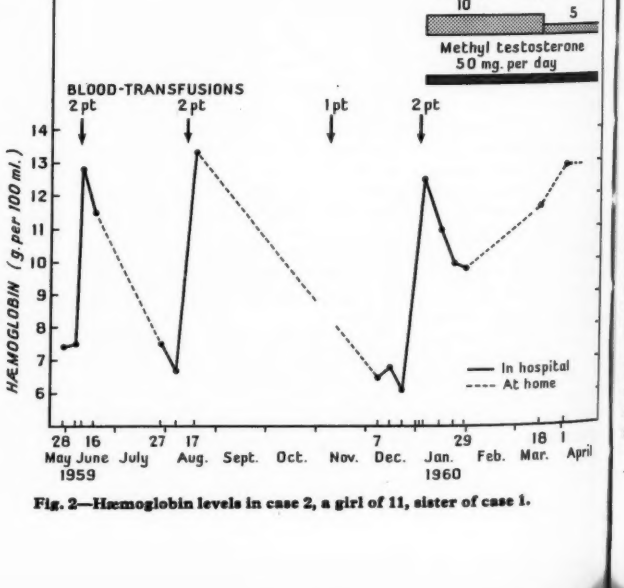


Fig. 2—Hæmoglobin levels in case 2, a girl of 11, sister of case 1.

Addendum.—At the end of June, 1960, these children had been under treatment for 6 months, and in each case the hæmoglobin was over 13 g. per 100 ml. Bone-marrow activity was likewise satisfactory. In view of the good response to treatment, both drugs have been reduced in amount, and it is intended to discontinue therapy in a month or two. The blood-picture will thereafter be watched.

Thanks are tendered to Prof. F. J. Ford for advice and Dr. J. G. Burger, superintendent of Groote Schuur Hospital, for permission to publish this report, which is based on a paper presented to the 4th Congress of the South African Pædiatric Association in Cape Town on April 4, 1960.

Department of Child Health,
University of Cape Town, and
Groote Schuur Hospital,
Observatory, Cape Town. ROBERT MCDONALD.

POSTPARTUM PRE-ECLAMPSIA

SIR,—May I congratulate Flight-Lieutenant McFadyen on observing and describing the phenomena recorded as "postpartum pre-eclampsia" in your issue of Nov. 5? He will forgive me for pointing out that I did mention that such events do occur on pp. 164 and 243 of my book, *The Pregnancy Toxæmias*, and for the first time in your columns in 1932.[1]

Would it not be wiser to attribute all the "eclampsias" to disturbances in one or more of the homœostatic mechanisms rather than postulate a single cause for one or all of them?

Bradford. G. W. THEOBALD.

PERITONEAL SPLASH: A PHYSICAL SIGN

SIR,—The letters by Mr. Lane Roberts (Sept. 24) and Mr. Smiddy (Oct. 15) interested me, particularly because I have found it useful to try to elicit the presence of fluid in doubtful perforation.

My custom in such doubtful cases is to auscultate the abdomen for bowel sounds, and the patient is asked to cough. If there is fluid and air in the abdomen then a double sound is heard as the wave of fluid is displaced by contraction of the diaphragm. The nearest English equivalent I can suggest is "tch-tch." When this is heard one can be confident that there is air and fluid in the abdomen, but it is not heard in every case, particularly in early perforation when there may be little fluid.

Weymouth and District Hospital. J. JEWERS.

PULLED SHORT EXTENSORS

SIR,—I should like to describe briefly a new differential diagnosis of twisted ankle or foot—"pulled short extensors".

Since most patients have heard of twisted ankles many arrive in the casualty department with a history of having fallen and twisted their ankle. So severe is the initial pain that many arrive in the casualty consulting-room in a wheel-chair.

The injury can happen at any age. In the cases I have reviewed the age-range is 11 to 64 years. Nearly 25% of all foot and ankle injuries in the period May to December, 1959, were of this kind. *Clinical examination* shows considerable swelling over the dorsum of the foot near the origin of the extensor digitorum brevis. No swelling of the ankle-joint is seen or palpable, and there is no tenderness over the styloid process of the 5th metatarsal bone. *Radiographic findings* are negative. One patient had ruptured short extensors associated with a fracture of the sustentaculum tali.

A cold compress of lotio plumbi or saline is applied, and on the first day of the injury the patient rests at home. Seen in casualty again on the third day after injury, they have all recovered and are discharged—in contrast with the ankle sprain, which may require treatment for two weeks or more.

Bedford General Hospital. K. A. TAYLOR.

1. *Lancet*, 1932, ii, 1380.

SPONTANEOUS FRACTURE OF THE FIBULA

SIR,—Mr. Maudsley (Nov. 5) has, I think, oversimplified the explanation of "fatigue" fractures both in the fibula and in general.

First, in the fibula, these fractures occur in infants, children, adolescents, young adults, and in middle age. Secondly, I do not feel it is right to compare fatigue in living bone to fatigue that occurs in other materials, such as metal. Undoubtedly a dead bone will suffer fatigue, but we have no good evidence that true fatigue occurs in normal healthy living bone.

It is therefore presupposing the pathological changes to call these lesions fatigue fractures and it is wiser, in my opinion, to call them stress fractures.

Stress Fracture Bureau,
Middlesex Hospital,
London, W.1. M. B. DEVAS.

MODERN CLINICAL BIOCHEMISTRY

SIR,—Dr. Osborn's letter (Nov. 5) is the best argument that has yet been put forward for the establishment of independent biochemistry departments controlled by qualified scientists.

His views are no more than we can expect from one who admits that he is prepared to put the clock back for more than a century, but what a pity it is that Virchow's attitude of 1855 should still dominate the minds of some pathologists. Ehrlich was a great man, and amongst his numerous claims to fame stands the fact that he was the founder of chemotherapy, which is not the same as clinical biochemistry. And what Tolstoy wrote in his *Tales* of 1903 is little to the point in a discussion on Modern Clinical Biochemistry. If Dr. Osborn would care to read something rather more recent, I would recommend the article in *Clinical Chemistry* last month by Prof. J. G. Reinhold entitled The Professional Status of Clinical Chemists. If he studies this excellent address, he may realise that there may be more than one side to a question.

When Dr. Osborn ranks the biochemist equally with the senior technician in the other subjects, he certainly does shock me; but he does not surprise me. Many pathologists hold this view, but at least it is something of an improvement on Professor Cappell's description of biochemists as "other workers not medically qualified" and every little helps. A little plain writing does a world of good, and Dr. Osborn's contribution must have opened quite a few eyes. Indeed, it is questionable whether he or I will do more on behalf of clinical biochemistry in its efforts to free itself from the pathological mentality of last century.

In reply to Dr. Pinkerton (Nov. 5) I would say that if he, or anyone else, still believes that I have overstated the case, surely Dr. Osborn's letter will convince him that the case has been severely *understated*. Why should Dr. Pinkerton think it "patently absurd" that each large hospital should have an independent biochemistry department? Many large hospitals in Edinburgh, Glasgow, and elsewhere have independent biochemistry departments and they maintain a high standard of work. Such departments have the great advantage that clinicians can approach the biochemist directly on any biochemical problem without the intervention of the pathologist, and vice versa. It is a system which works with the minimum of trouble and might be copied elsewhere with considerable advantage.

I have neither said nor implied that the biochemist should "go it alone" or work in a "watertight" department, and I know of no professional clinical biochemist who would support such an idea. The modern clinical biochemist works in the closest cooperation with all clinical units by contributing his share of specialised work directly to the clinician in charge of the patient. The clinician, *and the clinician alone*, is the one to decide on matters of diagnosis and treatment.

Dr. Pinkerton's letter comes near to the suggestion that has often been made recently—that some new nomen-

clature is sadly needed. It would appear that "Pathology" has at least three different meanings:

(1) Pathology in the academic sense of morbid anatomy plus morbid histology which, whatever its failings as a definition, ensures that we know what we are talking about.

(2) The pathology which not only includes the above, but which also has dominion over other, quite separate, subjects, such as biochemistry. This may have been a good thing at the start of the century but it is hopelessly out of date today.

(3) The pathology which claims to be the study of disease and to cover all aspects of "medicine" as well as many of the sciences. Such an omnibus definition would have no real meaning.

A little clarification would save a good deal of ill-feeling. But pathologists should beware of the term "integration". Far too often this mathematical term is apt to be confused with the expression "empire building" and does not inspire confidence.

Department of Biochemistry,
Western Infirmary,
Glasgow, W.1. E. B. HENDRY.

SIR,—May an obscure, humble, and wholly incompetent non-medical biochemist express grateful thanks to Dr. Hendry (Oct. 29) and Dr. Woolf (Nov. 12) for helping to banish the gloom induced by the Protocols of Professor Cappell (Oct 15)? Indeed, Dr. Woolf's comments are so identical with my own that I feel we must be in telepathic contact.

I do not feel, however, that giving high-calibre scientists the privilege of ordering their own equipment or appointing their own staff (as enjoyed by, say, pharmacists or almoners) will attract them into the hospitals. They will still have to contend with medically sycophantic nurses and administrators and will be either treated with contempt as irresponsible schoolboys or patronised as talented court jesters. The stigma of being "non-medical" will never be eradicated; and it will be better for this country if its first-class brains are used in the cause of economic survival rather than frittered away on the trivialities of modern clinical biochemistry as practised in hospitals today.

Swansea. E. B. LOVE.

MYOCARDIAL INFARCTION DURING PREGNANCY AND PUERPERIUM

SIR,—We were very interested in the paper of Sept. 3 by Dr. Watson and his colleagues and should like to add an unusual case of our own.

A 35-year-old Jewish Yemenite woman, 11 years in Israel, mother of 7 children, was admitted to our department in February, 1960, because of dyspnœa and cough. She had been pregnant 12 times, aborted 3 times, and 2 of her children had died while in Yemen. She had never been ill or suffered chest pain before. Thirty days before admission she had given birth at term to a normal infant; there had been slight swelling of the feet during her pregnancy but otherwise it had been normal. She had been well until the night before admission when she awoke with a feeling of oppression in the chest and breathlessness.

We found an anxious, pale, and cyanosed woman with pulmonary œdema. Her pulse was regular at 120 per min., a systolic murmur grade I–II was heard over the precordium, and the liver was enlarged 3 cm. beneath the costal margin. Her blood-pressure was 125/100 mm. Hg, the erythrocyte-sedimentation rate was 75/110, the V.D.R.L. flocculation test was negative, total serum-cholesterol 292–312 mg. per 100 ml., serum-proteins within normal range. An X-ray of the chest confirmed the pulmonary œdema.

The electrocardiogram on admission showed an incomplete left bundle-branch block. E.C.G. tracings during the following days showed that the left bundle-branch block had disappeared and been replaced by the pattern of anterior septal infarction: deep Q waves in V_1, V_2, V_3 with dome-shaped ST segments and negative coronary T waves. Further E.C.G. tracings revealed the usual dynamics of myocardial infarction. The patient was given digitalis and diuretics for the pulmonary œdema, but otherwise she recovered from her attack without specific treatment.

She remained under our observation because of repeated precordial pains which gradually disappeared. The laboratory findings returned to normal: the blood-pressure fell to 100/70, the erythrocyte-sedimentation rate to 20/40, and the serum-cholesterol to 192 mg. per 100 ml. The liver diminished in size. Further X-rays of the lungs and heart, barium meal, and intravenous pyelogram were normal. She has since resumed her activities as a housewife.

Not only is this one of the rare cases of myocardial infarction in the puerperium, but it is also rare to find myocardial infarction in a Yemenite woman. During the past ten years we have seen in this department 1063 cases of myocardial infarction (835 men and 228 women), but never before in a woman in the puerperium or in a Yemenite woman before the menopause. The incidence of myocardial infarction is generally very low [1–5] in Yemenite Jews, the disease being practically unknown among those Yemenites who came to Israel since 1949.

Brunner et al. and Toor et al.[6] compared the serum-lipid levels of the different communities in Israel and found very low cholesterol levels in those who came to Israel from Yemen recently. According to Toor et al. the mean total serum-cholesterol for Yemenite women of the age of our patient (35–44) is 172 ± 26 mg. per 100 ml. It is significant then that our patient had a high serum-cholesterol level of 292–312 mg. per 100 ml. at the time of her attack, which fell to 192 after her recovery.

All our attempts to find one of the unusual causes of myocardial infarction in this case were unsuccessful. This was probably therefore an "atherogenic" occlusion of a coronary artery.

HARRY BASSAN
Department of Internal Medicine A, JOSEPH K. KAFTORI
Rambam Government Hospital, YAAKOW KOGAN.
Haifa, Israel.

CHRISTMAS GIFTS FUND APPEAL

SIR,—I should like to remind your readers who have not yet responded to the chairman's appeal that it is our custom to distribute the gifts some days before Christmas.

I hope all who can will send their contributions marked "Christmas Gifts" to the Royal Medical Benevolent Fund, 37, St. George's Road, Wimbledon, London, S.W.19, as soon as possible.

GEOFFREY H. BATEMAN
Honorary Treasurer,
Royal Medical Benevolent Fund.

LOOKING AFTER NURSES' CHILDREN

Dr. N. F. COGHILL, chairman of the West Middlesex Hospital medical committee, writes:

"Many hospitals short of nurses employ married nurses part-time and find them a great help. Such nurses can more easily return to hospital work if their children are satisfactorily cared for during the day. We have been thinking of starting a creche-cum-nursery-school at the West Middlesex Hospital, Isleworth, for the children of married trained nurses. I would be most grateful to hear from anyone who has had experience of such a scheme and its difficulties."

1. Dreyfuss, F. *Amer. Heart J.* 1953, **45**, 749.
2. Brunner, D., Loebel, K., Fischer, M., Schick, G. *Harefuah*, 1955, **48**, 1.
3. Brunner, D., Loebel, K. *Lancet*, 1957, i, 1300.
4. Brunner, D., Loebel, K. *Ann. intern. Med.* 1958, **49**, 732.
5. Brunner, D., Manelis, G., Loebl, K. *Lancet*, 1959, i, 1071.
6. Toor, M., Katchalsky, A., Agmon, J., Allalouf, D. *ibid.* 1957, i, 1271.

Parliament

Judicial Corporal Punishment

BECAUSE there seemed to be considerable support in the country and in Parliament for the reintroduction of corporal punishment as a judicial penalty, the Home Secretary at the beginning of this year asked his Advisory Council on the Treatment of Offenders to consider whether there were any grounds for doing so. Corporal punishment was abolished in 1948 and it was suggested that a review of the matter was desirable in the light of post-war trends in crime and of current opinion in the treatment of offenders. In their report,[1] published this week, the Council admit that at the outset of their inquiry some of their number felt that the reintroduction of this form of punishment might be justified as a means of checking the growth of crime in general and of hooliganism in particular. But after considering all the evidence put before them they had unanimously come to the conclusion that " corporal punishment should not be reintroduced as a judicial penalty in respect of any categories of offence or of offenders."

They found that there was a cleavage of opinion, not only among the general public but also among people of knowledge and experience, whether the penalty should be reintroduced or not and also great divergence of views on such aspects of the problem as the offences for which it should be imposed and the groups of offenders to whom it should be administered. Though all admitted that it would be a retrograde step, the Council thought that it was not generally realised how retrogressive it would be. Corporal punishment was only abolished in 1948, but between 1861 and 1948 it was in fact only available for adults for robbery with violence. To reintroduce it, as some proposed, for all offences of violence against the person, in particular those committed by young hooligans, would mean "putting the clock back not twelve years but a hundred years."

The Council also point out that we are the only country which demands its reintroduction, and that to do so would damage our reputation as pioneers of enlightened methods of penal treatment. Nor do the Council believe that there is any assurance that its reintroduction would substantially reduce crime. They have found no evidence that it is an especially effective deterrent either to those who have received it or to others. Though, like many forms of drastic and severe punishment which have been abolished " as affronting the conscience of a civilised community ", it would deter a few, the Council are not satisfied that the numbers would justify a form of punishment with so many disadvantages, which is not in tune with modern penal methods, and which would militate against the success of reformative treatment.

Many of the new methods introduced under the 1948 Act have not yet been fully tried and are likely to greatly develop in the future, when, for example, more detention centres have been opened. In the Council's view it is, therefore, too soon to conclude that these methods are inadequate. The Council also found that practical difficulties and objections, especially the inevitable delay between the commission of the offence and the infliction of the punishment, strengthen the case against judicial corporal punishment. Their conclusions will, they realise, be more readily accepted if alternative methods of checking crime are introduced; and, though it was not part of their task to suggest such measures, they mention that they were impressed by the arguments of many of their witnesses that the greatest deterrent is not fear of punishment but certainty of detection. This, they point out, can only be achieved by a fully staffed and efficient police force in all areas. They also noted a widespread feeling that the courts sometimes seemed to deal surprisingly leniently with offenders convicted, often not for the first time, of offences of violence. Though the Council realise that there may often be good reasons for this, they suggest that there are cases in which " a severe and exemplary punishment is often salutary ". They consider that the courts already have adequate powers to meet this need. They end their report with the hope that their own recent recommendations for the treatment of young offenders [2] will be implemented before long. They are convinced that these and the methods contemplated by the 1948 Act are likely to prove " more effective in the long run than negative methods such as corporal punishment ".

1. Corporal Punishment. Cmnd. 1213. H.M. Stationery Office. 1960. Pp. 58. 3s. 6d.

Finances of Scientific Societies

In the debate on scientific policy in the House of Lords on Nov. 9 Lord ADRIAN drew attention to an unexpected, and perhaps unintentional, difficulty which independent scientific societies may soon have to face. Because of a proposed change in the way they are rated, the help they get from the State may be reduced.

Progress in both pure and applied science, he believed, was immensely helped by all these independent bodies that had grown up, some to encourage particular branches of science, like the Chemical Society or the Geological Society, and some to encourage science in general, like the Royal Society and the British Association. They had been the main forum for the interchange of ideas. They had meetings and libraries. The Royal Society of Medicine, for instance, had the best medical library on this side of the Atlantic. They published their own journals, and they became the representative bodies that rewarded merit and could be called on for advice. They began, like most of our hospitals, supported entirely by voluntary contributions; but for more than a hundred years they had been assisted by the State in the provision of buildings for some of them, by exemption from rates, and recently by grants for publications. It had been a thoroughly British arrangement. They had kept their freedom and independence, but the help they got from the State made it possible for them to shoulder the much greater responsibility they had to face nowadays when science grows overnight.

There was no serious complaint about the way the arrangement had been working recently, or about the good will of the Government toward the scientific societies; but they had lately become aware of a danger threatening their finances, and the finances of none of them were very large. Part of the aid which the State had given them had been in the form of exemption from rates, because the societies had come under the heading of a special kind of charity. But the system by which charities were rated was full of inconsistencies and needed to be tidied up. The Pritchard Committee had considered how to do the tidying up, and one of its proposals was that, in future, the societies which were now exempt ought to be made to pay half the full rateable value of their premises. (The scientific societies would not be the only sufferers, but Lord Adrian admitted that he was leaving the Arts to look after themselves.) If the scientific societies had to shoulder these new burdens without any increased help, they must put up their subscriptions and cut down their expenses—that is to say, cut down the journals they published and the meetings they arranged. If this change took place, no doubt the large national societies would survive. But some of the smaller bodies, which look after highly specialised branches of science, might be faced with extinction, and we might find ourselves paying too high a price for a tidy system of rating.

In the course of his reply to the debate Viscount HAILSHAM promised that he would look into the rating of the learned societies. The question was under consideration by the Government, but he was not sure what the answer would be. There were difficulties in the way of exemption from any tax. However, he saw the force of what Lord Adrian had said.

Public Health Bill

This Bill, which was published on Nov. 11, provides for the replacement of local building by-laws by regulations made by the Minister of Housing and Local Government and applicable throughout England and Wales outside the county of London. It would also amend the Public Health (Drainage of Trade Premises) Act, 1937, to enable local authorities to charge for the reception into the public-sewerage system of some trade

2. Treatment of Young Offenders. H.M. Stationery Office. 1959.

effluents at present exempt, and it would classify as "trade effluents" farm effluents and effluents from premises used for scientific research. It would empower the Minister to remove the exemption given to laundry effluents under the 1937 Act where their discharge would be likely to cause special difficulties in the treatment or disposal of sewage. The Bill also incorporates into the general law some public-health provisions already included in local Acts. These are for the most part modest extensions or adaptations of existing statutory provisions which the experience of local authorities has shown to be necessary, and deal with such matters as sewers and drains, water-supply, infectious diseases, streets, and parks and open spaces.

QUESTION TIME

Foot-and-mouth Disease

Mr. D. G. BULLARD asked the Minister of Agriculture, Fisheries, and Food if he would make a statement about the present serious outbreak of foot-and-mouth disease.—Mr. CHRISTOPHER SOAMES replied: During the past eight days, 94 outbreaks of foot-and-mouth disease have occurred in parts of Eastern England and Scotland. The most seriously affected areas are in Norfolk and Suffolk and in Northumberland, and wide movement restrictions have been imposed in East Anglia, Northumberland, Durham and in most of Scotland because infected cattle are known to have passed through markets in these areas. My veterinary staff are doing their utmost to trace the origin of the outbreaks, but so far there is no clear indication of the cause.

Doctors Overseas

Mr. L. A. PAVITT asked the Minister of Health what consultations had taken place with the Colonial and Commonwealth Relations Offices to facilitate the acceptance by doctors of posts overseas and their subsequent reabsorption into medical service in the United Kingdom.—Mr. POWELL replied: I am not aware of any special obstacle to the reabsorption into medical service here of doctors who have taken posts overseas.

Obituary

JOHN WALTER LENNOX SCOTT

C.B., D.S.O., M.R.C.S.

Major-General John Scott, who died on Nov. 6 at Crookham, was director of medical services in the British Expeditionary Force at the beginning of the late war. After he retired from the Service he took charge of the large E.M.S. hospital at Park Prewett.

He was born in 1883 and was educated at Dulwich College and Westminster Hospital. He qualified in 1905 and a year later joined the R.A.M.C. During the 1914–18 war he served in France and Belgium and was three times mentioned in despatches. In 1918 he was awarded the D.S.O. From 1926 to 1930 he was deputy assistant director-general at the War Office. Later he became successively assistant director-general and deputy director-general of Army Medical Services. He was advanced to the rank of major-general in 1937, and became D.D.M.S., Eastern Command. On his retirement in 1941 he was appointed C.B.

R. E. B., who as D.D.M.S. in Southern Command made arrangements with Scott for the reception of casualties at Park Prewett, writes:

"Those were anxious days, with some 10,000 casualties arriving from the beaches in L.S.T.s and other craft. Later there were airborne evacuations and shiploads of invalid ex-prisoners of war from Japan and Germany. During this period Park Prewett, the largest hospital in the command, was our great stand-by. General Scott met the almost daily crises completely unperturbed, and the whole vast organisation worked with clockwork efficiency. Never once did I appeal for his help in vain. I never failed to receive his wholehearted support and kindly advice. The part he played in these crucial years was a fitting end to a distinguished career."

General Scott leaves a widow and two sons.

HENRY LEO BARNIVILLE

B.A., M.D., M.Ch. Dubl.

Emeritus Professor Barniville, senior surgeon to the Mater Misericordiæ Hospital in Dublin, and a senator of the Irish Free State, died in Dublin on Sept. 23, at the age of 73.

From Rockwell College, Co. Tipperary, he entered the medical school of the Old Catholic University in Cecilia Street. He took his M.B. with first-class honours in 1911 in the National University of Ireland when University College, Dublin, was founded as a constituent college. After spending a year as house-surgeon in the Mater Misericordiæ Hospital, he won the first medical travelling studentship offered by the new university. With it he spent two years in Freiburg in Breisgau and a year in London in the Cancer Hospital in Fulham Road. In 1915 he returned to Dublin as assistant surgeon to the Mater Hospital. In 1918 at the age of thirty-two he succeeded to a vacancy on the senior staff. In 1925 he succeeded to the chair of surgery at Dublin University College. He was nominated to the first Senate of the Irish Free State, and he remained a member until the Senate was abolished in 1936. On its reconstruction in 1938 he was elected to represent the graduates of the National University and he continued to represent them. In 1947 he sustained a detachment of the retina. Though it was successfully operated on, he had to give up many of his outdoor pursuits and lead a life of restricted activity.

A colleague writes:

"Barniville's remarkable gifts and exceptional start in his professional career promised a future that was only partly fulfilled. He never wrote anything and he never made a communication to the Academy of Medicine. This is the more regrettable because he had accomplished much. By the early forties he had over 500 cases of toxic goitre operated on with negligible mortality under the crude anæsthesia of that time. The reasons for this omission are both simple and complex.

"He reached success too early and by the age of thirty-five was working so hard that he had scarcely the time for anything except work. Dublin hospitals at that time were grossly understaffed with registrars and assistants, so that the drudgery of record-keeping and case-collecting had to be done personally by anyone who was preparing to write.

"He was the kindest and most charitable of men, as many generations of students whom he helped could testify. He was always a good and witty companion, and those who met him in his early years long cherished his memory. He loved good company, a race meeting, a game of bridge, which he played with distinction, and the almost lost art of conversation. In his professional work he had beautiful hands, a rare feeling for tissue, and imperturbable good humour which enabled him to ride out any storm. His approach to the nervous or difficult patient was wonderfully reassuring, and when he had taken his patient's hand in his own and sat down beside the bed and spoken only a few words the relief of tension was immediate."

In 1910 Professor Barniville married Miss Brigid Weymes by whom he had three children, the youngest of whom is a doctor.

HAROLD STUART BARBER

M.D. Dubl., F.R.C.P.I., M.R.C.P.

Dr. Stuart Barber was one of the few physicians in this country who gave almost all his time to the care of patients with rheumatic diseases, and he played an important part in developing the rheumatology services in the Manchester region. He died on Nov. 8 at the age of 49.

He qualified from Trinity College, Dublin, in 1933 and almost immediately joined the R.A.F. medical branch. He

served as a medical specialist throughout the war but soon afterwards returned to civil life. He held resident hospital appointments in London at the Prince of Wales' Hospital, Tottenham, and in the skin department at St. Bartholomew's Hospital before settling in Buxton, where he succeeded Dr. C. W. Buckley. He was also assistant clinical director of the rheumatism research unit at the University of Manchester.

In 1948, when the National Health Service was started, Barber was appointed consultant physician to Withington Hospital, Manchester, and the Devonshire Royal Hospital, Buxton. He was a member of the Heberden Society and made many valuable contributions to clinical rheumatology, including papers on the psychogenic basis of some so-called rheumatic pains, the use and misuse of physiotherapy, and a myalgic syndrome. His last paper, a report of an unusual form of familial osteodystrophy, appeared in our columns in June.

Of his work in the region J. H. K. writes:

"At his hospitals Barber practised rheumatology as a specialty within medicine and was largely responsible for the conversion of the Devonshire Hospital, Buxton, from an outmoded spa hospital into a modern centre for the treatment of rheumatic diseases with an international reputation. He faced his long illness with great courage and worked until two weeks ago. He was a most courteous and thoughtful man who loved the Derbyshire countryside in which he lived and which his wife paints most effectively."

Public Health

Maternity Services in Glasgow

In Glasgow last year less than 60% of parturient women were confined in hospital. In his annual report Dr. W. A. Horne, the city's medical officer of health, expresses disappointment that no progress was made during the year towards increasing this proportion, which, he says, should be not less than 75%, in order to secure the admission of all women who should be confined in hospital either for medical or for social reasons. The regional hospital board has formulated plans for new maternity hospitals and for the provision of maternity beds in existing hospitals. "Up to date not one additional bed has been provided, although some 90 beds are due to be available within a period of six months."

The perinatal mortality-rate for Glasgow was 45·5 per 1000 live and still births—a higher rate than that for any other city in Scotland or England.

Food-poisoning due to *Cl. welchii*

Outbreaks of *Clostridium welchii* food-poisoning continue to be reported.

In Edinburgh [1] 30 guests had diarrhœa and abdominal pain between eleven and eighteen hours after a wedding reception. Suspicion fell on steak pie, prepared on the previous day from 30 lb. of stewing beef, which was all heated in a pot for an hour and a half, and then left with the lid off for eighteen hours in the kitchen. On the morning of the wedding-day it was heated again for about three-quarters of an hour. Four hours later—half an hour before the meal was served—the cook noticed that the meat smelt sour and had a peculiar taste. He consulted the butcher, who, after stating that he had experience of cooking, put the meat in a colander and washed it under the tap. Fresh gravy was made from gravy powder, and the meat was heated once more and served with pastry as steak pie. Heat-resistant *Cl. welchii* was isolated from the stools of the patients.

Another outbreak affected 77 pupils, 10 teachers, and 4 kitchen workers at a school. In this case mutton was to blame; it had been steamed on the day before consumption and left to stand overnight in a pantry.

1. Annual report of the Public Health Department, Edinburgh, for 1959.

In 273 out of 723 cases of food-poisoning in Lancashire in 1959, *Cl. welchii* was the causal organism.[2]

At Dagenham [3] 98 children and 13 staff-members at a junior school were taken ill after eating lamb which had been cooked at another school. The bacteria multiplied in the two hours before the meat was eaten.

The following measures [4] will help to avert this form of food-poisoning:

Meat should be cooked so that heat-resistant spores are destroyed. Pressure-cooking is helpful; and joints should be thoroughly roasted.

If not eaten at once, the meat should be rapidly cooled and left in a refrigerator till required.

When meat is kept warm before being served, the temperature of the hotplate should be maintained at 60°C.

Notification of Anthrax

From Dec. 1 anthrax will be notifiable by medical practitioners to the medical officer of health of the district.[5] Cases of this disease in factory workers are already notifiable to the chief inspector of factories; and in future such cases will also be notifiable to the medical officer of health.

2. Report of the medical officer of health for Lancashire for 1959.
3. The health of Dagenham in 1959: annual report of the medical officer of health.
4. *Med. Offr*, 1958, **99**, 340.
5. Public Health (Infectious Diseases) Amendment Regulations, 1960. S.I. 1960, no. 1989. H.M. Stationery Office. 2*d*.

Appointments

CLARK, J. R., M.B. Edin., M.R.C.P.E.: consultant physician, Borders hospital group.
FRASER, M. S., M.B. Edin., M.R.C.P.E.: consultant in medical pædiatrics, East Fife hospital group.
MURPHY, LORETTA P., M.B. N.U.I., D.P.H., D.C.H.: assistant M.O., Leicestershire.
SPENCE, A. J., M.B. Aberd., F.R.C.S.: consultant orthopædic surgeon, East and West Fife hospital groups.

The Hospital for Sick Children, Great Ormond Street, London:
ECKSTEIN, H. B., M.D. Cantab., F.R.C.S.: surgical registrar.
FRY, H. J. H., M.B. Sydney, F.R.C.S.: house-surgeon, orthopædic and plastic department.
GOODALL, JANET, M.B. Sheff., D.OBST., D.C.H.: house-physician.
HARRIS, LEWIS, M.B. Glasg., D.P.M.: resident registrar, neurological and neurosurgical departments.
SMITH, CLARE NEVILLE, M.B. Cantab., D.P.H.: assistant R.M.O., Tadworth.

South Western Regional Hospital Board:
BRADFIELD, A. M., M.B. N.Z., M.R.C.P., D.P.M.: consultant psychiatrist, South Somerset clinical area.
MCNULTY, M. R., M.B. N.U.I., F.F.R., D.M.R.D.: consultant radiologist, Bath clinical area.
MONTGOMERY, J. N., M.D. Belf., M.R.C.P., D.C.H.: consultant pædiatrician, Plymouth clinical area.

Western Regional Hospital Board, Scotland:
AITCHISON, J. D., M.B. Glasg., F.R.F.P.S., M.R.C.P.: consultant physician, Stirling Royal Infirmary and associated hospitals.
BARBER, N. K., M.B. Leeds, F.R.F.P.S.: consultant ophthalmologist, Glasgow Eye Infirmary.
BRODIE, WILLIAM, M.B. Glasg., F.R.F.P.S.: assistant orthopædic surgeon, Glasgow Royal Infirmary.
CAMERON, J. H., M.B. Glasg.: assistant ophthalmologist, Ayrshire area.
CHERINGTON, F. J., M.B. Glasg.: assistant ophthalmologist, Glasgow Ophthalmic Institution and Ayrshire area.
CHISHOLM, E. A., M.B. Glasg., F.R.C.S.E., F.R.F.P.S.: consultant orthopædic surgeon, Dumfries and Galloway Royal Infirmary and associated hospitals.
CRAWFORD, J. M., M.D. Glasg., M.R.C.O.G., D.P.H.: consultant obstetrician and gynæcologist, Falkirk and District Royal Infirmary and associated clinics.
CUTHBERT, RICHARD, M.B. Glasg., D.M.R.D.: consultant radiologist, Stirling and Falkirk areas.
DEMPSTER, W. H., L.R.C.P.E., D.M.R.D.: consultant radiologist, Law Hospital, Carluke.
DYKES, W. S., M.B. Glasg., F.F.A. R.C.S., D.A.: consultant anæsthetist, Western Infirmary, Glasgow, and associated hospitals.
GIBB, MURIEL E., M.B. St. And.: assistant E.N.T. surgeon, Glasgow Royal Infirmary.
LAMB, ROBERT, M.D. Glasg., M.R.C.P.E., D.P.H.: consultant in infectious diseases, Renfrewshire area hospitals.
MCGOVERN, G. P., M.B. Edin., M.R.C.P.E.: assistant psychiatrist, Stobhill General Hospital, Glasgow.
MORRISON, A., M.B. Edin.: assistant orthopædic surgeon, Law Hospital, Carluke.
PASIECZNY, T. A. H., M.D. Warsaw: assistant dermatologist and venereologist, Glasgow Royal Infirmary, with duties at Glasgow venereal-disease clinics.
ROBERTS, G. B. S., M.D. Glasg.: consultant pathologist, Ayrshire area hospitals.
SMITH, MARY D., M.D. Glasg., F.R.F.P.S., M.R.C.P.E.: consultant pathologist (hæmatology), Stobhill General Hospital, Glasgow.
THOMSON, W. S. T., M.B. Glasg.: consultant biochemist, Southern General Hospital, Glasgow.
WILSON, THOMAS, M.B. Glasg., F.R.C.S.E.: consultant ophthalmologist, Glasgow Eye Infirmary.

Notes and News

THE HOSPITAL "SERVICE"

IN opening a three-day conference at Peebles on Nov. 7, Lord Craigton, Minister of State for Scotland, asked how far the "hospital service" was in fact a service. "It is all financed in one way; boards are appointed in the same way; members of each profession or grade of staff work on the same conditions and the same rates of remuneration. In many ways the extremer variations in the standards of service for the patients that existed before 1948 have been removed. And we have made some progress in reorganising and rationalising the pattern of the hospital and specialist services on the lines that were so widely advocated before 1948 . . ." On the other hand, there were still too many substantial differences in the scale of hospital provision; and a national service, paid for mainly out of taxation, could not normally justify such wide variations unless they were clearly necessary.

Scotland, Lord Craigton pointed out, had five regional boards and over 80 boards of management all with the same duties and functions. Yet there were remarkable differences in the way they approached their job—in the committee structure, in the frequency of meetings, in delegated authorities, and even in the kind of things on which members concentrated their attention. "I find it hard to believe that *all* these differences are desirable and that everybody must be right *all* the time."

Again, every hospital board was an employing authority advertising and appointing to its own posts. Hence the individual doctor, or nurse, or administrative officer, who was trying to obtain the right experience at the right time, faced career problems which he would not find in some of the other services, or even in some of the larger industrial undertakings. In the long run it was in the interests of all the employing hospital authorities that a man or woman should be able to get this variety of experience; "but can the particular employer who is concerned only to fill a particular post take this wider view?"

Every hospital was different; but should they be quite so different as they were? By this time we ought to have formed a clearer idea of what should be the standard of good practice. As soon as people got down to the detailed planning of new hospitals and new units within hospitals, questions began to be asked, to which there was no considered answer as to what should be the generally accepted standard. "I am not suggesting for a moment that we can achieve or want a uniform standard or a uniform pattern that everybody must observe rigidly. But it would be ridiculous and wasteful for every small group up and down the country to take each and every problem and work out their own solutions independently. There ought to be some basic generally accepted doctrine which they can take as a starting-point and from which variations and adjustments can be made to suit their own particular circumstances."

In conclusion Lord Craigton said that, with the increasing complexity of modern treatment, people would have to work more and more as a team, as was now evident in highly specialised hospital units. But this sense of membership of a team was spreading outside the hospital too, with growing emphasis on the outpatient department, peripheral clinics, domiciliary visits, and teamwork both with the family doctor and the other social services. In fact, "the individual hospital as a focus of loyalties and traditions has proved to be no longer enough. We are beginning to think more in terms of groups of hospitals serving communities and less in terms of what goes on inside the four walls of a particular building or cluster of buildings—of the services that the hospital provides rather than of the hospital itself."

He hoped that the hospital service would never be a service thought of in terms of discipline, uniformity, and chains of command. "But we have perhaps something to learn from these services in terms of group loyalties and as regards the common outlook on strategy and tactics which, when you come to analyse it, is really an underlying agreement on what the main problems are and how they ought to be tackled."

WORLD HEALTH ORGANISATION

AT a meeting in Geneva of the W.H.O. Executive Board, which opened on Oct. 25,[1] a working budget of $21,576,480 was recommended for 1962; of this, $110,033 was earmarked for health activities in the Congo. The Republic of the Congo (Brazzaville) and the Republic of Mali were admitted to full membership of W.H.O.

It was announced that the U.S.A. would give $4 million to the malaria eradication special account in 1961. A resolution supporting the full use by 1963 of Russian as a working language of the Regional Office and Committee for Europe was adopted.

APPOINTMENTS IN GENERAL PRACTICE

Appointment Systems in General Practice (35 mm. and 16 mm., sound, black-and-white, 31 minutes, Great Britain, 1960) is the second of a series of films on general practice in a modern society to be produced for the *Medical World*.

It consists of a photographic record of a discussion between a doctor who is using an appointment system in his urban practice, a family doctor with a country practice, and a woman representing the intelligent patient. Dr. Bruce Cardew is in the chair. The advantages, operation, and administrative details of the scheme are described and debated, and a case is made for the adoption of appointment systems more widely in general practice.

The film is probably intended to stimulate discussion, but family doctors who take the trouble to attend a meeting on the subject would like more information on the administration and costs. This could be more suitably presented by the printed word with reproductions of typical appointment cards and a page from an appointments book showing how space is allowed for the unexpected patient.

Copies of the film may be borrowed without charge from *Medical World*, 56, Russell Square, London, W.C.1.

A COT FOR THE ROOMING-IN OF NEWBORN BABIES

Dr. J. W. FARQUHAR writes from the Edinburgh University department of child life and health:

"The practice of accommodating the newborn baby beside his mother, and of making her largely responsible for his care, has made necessary the provision near her of clean napkins, baby gowns, cleaning materials, and such topical applications as dusting powder, oil, and cream. These should be personal to the baby. The mother's bedside locker can seldom take more than her own requirements, and the provision of an infant cotside locker, although effective, is expensive and space-occupying, and it increases the difficulty of floor cleaning.

1. See *Lancet*, Nov. 5, 1960, p. 1037; *ibid.* Nov. 12, p. 1097.

Fig. 1

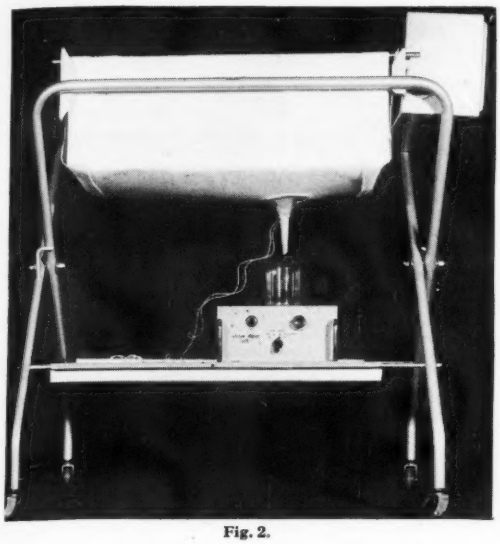


Fig. 2.

"The cot shown here (fig. 1), which is an adaptation of that known as the Liverpool Maternity Hospital pattern, has been designed for this purpose at the Elsie Inglis Memorial Maternity Hospital, Edinburgh. Strongly constructed and very stable, it has a tubular-steel folding frame mounted on well-running castors. The canvas crib is suspended longitudinally, on removable steel rods, and it can be readily adjusted to give a slight declination at the head end. It can be removed quickly, and is designed to facilitate laundering. Although the crib is open slightly at each corner, the baby is perfectly warm; the body heat has not been lowered in fullterm infants nursed in them.[1] The mattress, which is of latex foam, has a single faced hospital sheeting cover with zip fasteners.

"A small locker, 13 in. long, $5^1/_2$ in. deep, and 7 in. high, fitted to one end of the cot, has a closely fitting door, hinged at the top and held shut by a spring clip. The locker is large enough to take the necessary cleaning materials and topical applications, and high enough to accommodate a plastic thermometer case holding an individual rectal thermometer in antiseptic solution. The top of the locker has an identification-card holder. A larger locker of 20-gauge sheet steel, measuring 18 in. long, 10 in. deep, and 10 in. high, sits securely upon parallel steel rods below the canvas crib. The door of this locker is also hinged above so that it will close by gravity, and it has a strong spring clip. This locker provides adequate space for the day's supply of napkins, gowns, wraps, and blankets, and, at the Elsie Inglis Hospital where babies are weighed routinely on alternate days by spring balances, it also holds the personal knitted 'Terylene' mesh fabric net for suspension. Both lockers can be easily lifted off the cot for cleaning.

"The cot and all its fittings have a hard-baked enamel metallic finish, which is easily kept clean and which is resistant to antiseptic detergent cleaning agents. The cot, with canvas crib, two lockers, and the mattress, costs about £15.

"The cot is easily modified to collect urine from newborn babies. A hole is cut in the latex foam mattress (fig. 2) at a convenient point: for male infants, latex tubing strapped over the penis passes through this hole to the collecting bottle on a tray beneath the crib; for females a 4-in. polyethylene filter funnel is embedded in the mattress and its end passes through the canvas crib, either delivering into a beaker or being connected to a collecting bottle by latex tubing. The cot sheet has to be adapted for this purpose, and the hole is surrounded for some inches by light plastic sheeting which is folded into the funnel to prevent loss. When the baby is positioned properly, the ankles are lightly tied to the corners of the cot with crêpe bandage. A single thickness of nylon stocking is placed over a brass ring in the mouth of the funnel to catch any meconium which may be passed. An electrical alarm, which can be fitted to the funnel and accommodated on the tray, is so designed that the passage of a very small volume of urine will produce either urgent auditory or visual calls to the nursing staff in the room or at a remote station; they can then ensure that no urine is lost.

"I am grateful to Messrs. Spencer Mason, Ltd., for their cooperation; to Miss J. Beckett, matron of the hospital; to Miss J. Forrest, sister-in-charge of the newborn; and to Dr. J. M. Kerr, medical superintendent of the Edinburgh Southern Hospitals Group, for helpful advice. The filter-funnel technique of urine collection was modified slightly from that used at the Children's Medical Center, Boston, Mass, and the urine alarm unit was made for me by Mr. Eric Leask of the department of medical physics, University of Edinburgh. It will be described in detail elsewhere."

1. Farquhar, J. W., Ratcliffe, S. Report of the Elsie Inglis Memorial Maternity Hospital for 1959.

University of London

The title of professor of occupational health has been conferred on Dr. R. S. F. Schilling in respect of his post at the London School of Hygiene and Tropical Medicine.

Dr. Schilling, who is 49 years of age, was educated at Epsom College and St. Thomas's Hospital. After qualifying in 1934 he held house-appointments at St. Thomas's. In 1937 he became assistant medical officer at I.C.I. (Metals) Ltd. in Birmingham. In 1939 he became a medical inspector of factories. During the early part of the war he served with the R.A.M.C. In 1942 he was appointed secretary of the Industrial Health Research Board. In 1946 he was awarded a Nuffield fellowship in industrial health, and then he joined the Nuffield department of occupational health in the University of Manchester, at first as lecturer, and later became reader. His published work includes several papers on byssinosis in the cotton industry, and in 1956 he gave the Milroy lectures to the Royal College of Physicians of London, choosing as his subject chronic respiratory disease among cotton and other textile workers. In the same year he was appointed to his present post. He is a past president of the Association of Industrial Medical Officers. He has also served as editor of the *British Journal of Industrial Medicine*.

University of Sheffield

A course in dermatology for general practitioners will be held from March 20 to 24 at Sheffield Royal Infirmary. Further details will be found in our advertisement columns.

Royal College of Surgeons of England

At a meeting of the council on Nov. 10 with Sir Arthur Porritt, the president, in the chair, Dr. W. E. Lloyd was admitted to the board of examiners for the fellowship in the Faculty of Anæsthetists. Arrangements were made whereby the professorship of military surgery at the Royal Army Medical College should become a joint professorship with the Royal College of Surgeons.

Licences to practise and a postgraduate diploma were conferred on those named in the report of the comitia of the Royal College of Physicians in our issue of Nov. 5 (p. 1039).

Royal College of Physicians of Ireland

At recent examinations the following were successful:

M.R.C.P.I.—P. J. Faul, G. A. Kernohan.
D.Obst.—T. F. Canty, M. Ahmad-Genaidy.

Royal Society

One of the Royal medals of this society has been awarded this year to Sir Roy Cameron for his work on cellular pathology.

Chadwick Trust

On Thursday, Nov. 24, at 5 P.M., at 90, Buckingham Palace Road, London, S.W.1, Dr. R. Scott Russell, head of the radiological laboratory of the Agricultural Research Council, will give a Malcolm Morris lecture. His subject will be radioactivity in human diet.

Royal Society of Medicine

The Blair Bell medal for 1960 has been awarded to Prof. F. J. Browne, of Sydney. On Oct. 28, at a meeting of the section of obstetrics and gynæcology, his son, Prof. McClure Browne, received it on his behalf.

Charing Cross Hospital Medical School

On Thursday, Nov. 24, at 5.30 P.M., after the opening of the new surgical unit at the hospital, Prof. A. J. Harding Rains will give his inaugural lecture at the Royal Commonwealth Society, Craven Street, London, W.C.2. The title of the lecture will be A Chapter of Accidents.

Problems of Youth

The National Council for the Unmarried Mother and her Child will hold a discussion on this subject on Thursday, Jan. 26, at 5 P.M., at County Hall, Westminster Bridge, London, S.E.1. The chairman will be Dr. David Stafford-Clark.

Research Defence Society

On Tuesday, Dec. 6, at 5.30 P.M., at University College, Gower Street, London, W.C.1, Prof. J. H. Burn will give a Stephen Paget lecture. His subject will be Testing Drugs on Man.

International Embryological Conference

This conference will be held at the Middlesex Hospital Medical School, London, W.1, from Sept. 18 to 21. Particulars may be had, after May 1, from Dr. L. Brent, department of zoology, University College, Gower Street, London, W.C.1.

Road to Maturity

On Thursday, Jan. 26, at 10.30 A.M., the Central Council for Health Education will hold a conference on this subject. Further particulars may be had from the medical director of the council, Tavistock House, London, W.C.1.

Fulbright Travel Grants

Travel grants will again be available to citizens of the United Kingdom to go to the United States of America for academic or educational purposes. Full particulars may be had from the United States Educational Commission in the United Kingdom, 71, South Audley Street, London, W.1.

McGibbon Lectures

Dr. A. Rae Gilchrist will give the inaugural lecture of this series, instituted by the Scottish Radiological Society in memory of the late Dr. John P. McGibbon, on Saturday, Feb. 18, at 2.30 P.M. at the Royal College of Physicians of Edinburgh. He is to speak on radiological contributions to cardiology.

Molecular Basis of Neoplasia

This subject has been chosen as the theme of the 1961 symposium on fundamental cancer research which is to be held from Feb. 23 to 25 by the University of Texas M.D. Anderson Hospital and Tumor Institute. Further particulars may be had from the publications department, Texas Medical Center, Houston 25, Texas.

Stroke Rehabilitation

The Chest and Heart Association is to hold a conference on this subject on Friday, Dec. 9, at 2 P.M., at B.M.A. House, Tavistock Square, London, W.C.1. The speakers will include Prof. C. B. Perry, Dr. John Marshall, Dr. T. H. Howell, Dr. Denis Leigh, and Dr. Frank Cooksey. Further particulars may be had from the Associaton, Tavistock House North, Tavistock Square, W.C.1.

On Wednesday, Nov. 23, at 5.15 P.M., at the Royal Free Hospital, Gray's Inn Road, London, W.C.1, Dr. M. M. Suzman of Johannesburg will give a lecture on long-term use of anticoagulants.

On Friday, Dec. 2, at 8.30 P.M., at Whipps Cross Hospital, London, E.11, Superintendent G. E. Salter of New Scotland Yard will give a lecture on counter-criminal methods.

Sir Benjamin Rycroft is to be a guest speaker at an eye surgery clinical meeting which is to be held at the department of ophthalmology in the University of Toronto from March 20 to 22.

Heinz fellowships of the British Pædiatric Association have been awarded to Dr. H. B. Wong (Singapore), Dr. G. H. Holman (Saskatoon), and Dr. C. A. Reindorf (Toronto).

Diary of the Week

NOV. 20 TO 26

Monday, 21st

UNIVERSITY OF LONDON
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Prof. C. E. Lumsden: Pathology and Pathogenesis of Multiple Sclerosis.

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. Brian Ackner: Hysteria.

HUNTERIAN SOCIETY
8.30 P.M. (Apothecaries' Hall, Black Friars Lane, E.C.4.) Canon C. E. Raven, Mr. R. S. Murley (for); Mr. T. L. Marks, Dr. Fred Wrigley (against): That Advertising Does More Harm Than Good.

Tuesday, 22nd

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. D. A. G. Galton: Contributions of Chemotherapy to the Study of Leukæmia.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. C. D. Calnan: Effects of Chemical Agents, Primary Irritants and Sensitisers.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. (Wright-Fleming Institute.) Prof. Frank Goldby: Relation of the Nervous System to the Female Pelvic Organs.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Prof. A. G. R. Lowdon: Treatment of Acute Vascular Insufficiency In the Limbs.

MANCHESTER MEDICAL SOCIETY
4.30 P.M. (Medical School, University of Manchester.) Mr. A. R. Anscombe: Deaths of Three American Presidents.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIM
5.15 P.M. (General Infirmary at Leeds.) Mr. John Hankinson: Surgical Treatment of Parkinsonism.

ROYAL COLLEGE OF SURGEONS OF EDINBURGH, Nicolson Street, Edinburgh
5 P.M. Dr. Kristian Kristiansen (Oslo): Selective Cooling of Organs with Special Reference to the Brain.

Wednesday, 23rd

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.30 P.M. *Proctology*. Mr. R. W. Nevin: Review of Granulomata of Large Intestine. (Presidential address.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. Victor Wynn: Acid-base Metabolism.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. O. Oliver: Hæmopoietic System in Skin Diseases.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. T. Holmes Sellors: Diaphragmatic Hernia.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. Hugh Gough-Thomas: Research in the School Health Service.

WEST LONDON MEDICO-CHIRURGICAL SOCIETY, West London Hospital, W.6
8.30 P.M. Prof. A. J. H. Rains, Dr. Hugh Jolly, Miss Helen Mayer: Recent Advances in Treatment.

UNIVERSITY OF OXFORD
5 P.M. (Radcliffe Infirmary.) Prof. J. T. Ingram: Clinical Significance of the Minute Vessels of the Skin. (Litchfield lecture.)

UNIVERSITY OF LEEDS
5 P.M. (General Infirmary at Leeds.) Sir Andrew Claye: Forceps Today.
6 P.M. Miss U. M. Lister: Biochemical Changes in Pregnancy.

Thursday, 24th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. J. F. Nunn: Distribution of Inspired Gas During Thoracic Surgery. (Hunterian lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. H. B. Hewitt: Fundamental Aspects of the Radiotherapy of Cancer.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. Calnan: Cutaneous Allergy. (First of two lectures.)

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Dr. E. H. Mercer: Fine Structure of the Normal and Malignant Cell.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY
8.15 P.M. (11, Chandos Street, W.1.) Dr. M. N. Pai: Role of Hypnosis in Treatment.

CIBA FOUNDATION LECTURE
5 P.M. (Medical School, Edgbaston, Birmingham.) Dr. P. J. Thung (Amsterdam): Ageing in the Gonad-Adrenal System.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh.) Sir Stanford Cade: Synovial Sarcoma.

UNIVERSITY OF ST. ANDREWS
5 P.M. (Physiology Department, Queen's College, Dundee.) Prof. J. L. Malcolm: Pharmacological Dissection of the Central Nervous System.

Friday, 25th

ROYAL SOCIETY OF MEDICINE
4.30 P.M. *Pædiatrics*. Mr. W. J. W. Sharrard, Dr. C. O. Carter, Mr. J. A. Wilkinson, Mr. E. W. Somerville: Infantile Hip Disease.

POSTGRADUATE MEDICAL SCHOOL OF LONDON
10 A.M. Mr. Ian Fraser: Problems in Pædiatric Surgery.
4 P.M. Prof. A. Querido (Leiden): Goitrous Hypothyroidism.
5.30 P.M. Prof. W. W. Mushin: Controlled Respiration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY
4.30 P.M. Mr. Francis McGuckin: Ætiology of Chronic Otitis Media.

BRITISH TUBERCULOSIS ASSOCIATION
5 P.M. (Joint meeting with the British Association of Allergists at 26, Portland Place, W.1.) Dr. J. D. Everall, Dr. J. Morrison Smith, Dr. S. Z. Kalinowski, Dr. N. W. Horne: Hypersensitivity Reactions to Antituberculous Drugs.

BRITISH SOCIETY FOR IMMUNOLOGY
9.30 A.M. (183, Euston Road, N.W.1.) Opening of two-day symposium on Stimulation of Antibody Production.